PREFACE

In 1990, the Nordic Chemicals Group under the Nordic Council of Ministers started a project, the main aims of which were to coordinate the selection and evaluation of chemicals within the Nordic countries according to health effects. The project has now established a common basis for collecting and presenting data in order to obtain mutual acceptance of criteria documents prepared in the Nordic countries, thereby avoiding unnecessary duplication of work.

Criteria documents on health effects of twenty-one chemicals were presented by the Nordic Council of Ministers in the publications "Health Effects of Selected Chemicals" volumes 1 and 2 (Nord 1992:6 and Nord 1993:29). In this third volume eleven additional chemicals have been selected for evaluation of health effects on the basis of occurrence, use and distribution in the Nordic countries. Additional selection criteria have been discrepancies in the existing classification or evaluation of possible substitutes to more dangerous substances present on the market. Each criteria document has been prepared either by experts from the national authorities or by external consultants.

The work has been coordinated by a project committee consisting of representatives from the regulatory agencies and experts from four Nordic countries:

- Denmark: Lea Stine Tobiassen, Danish Environmental Protection Agency
- Finland: Katariina Ruuth-Rautalahti, National Product Control Agency for Welfare and Health
  Ritva Vuorinen, Ministry of Labour
- Norway: Erik Søderlund, National Institute of Public Health
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The criteria documents have been reviewed and compiled by the project committee. The different documents were prepared by:

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The project committee would like to express its gratitude to all who have participated in preparing the criteria documents in this publication.

BUTANE

CAS No: 106-97-8

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February 1994

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SUMMARY

n-Butane is a colourless, flammable gas at room temperature. It occurs as a component in natural gas from which it is refined. n-Butane is used as fuel, refrigerant and aerosol propellant.

The acute toxicity of n-butane has been studied after inhalation exposure in experimental animals. LC_{50} (4h) was 658 mg/l in rats and LC_{50} (2h) was 680 mg/l in mice. In dogs, lethal concentrations ranged from 474 to 592 mg/l. A concentration of 308 mg/l caused light anaesthesia in mice within 25 minutes, and an exposure to 521 mg/l had similar effect within one minute.

n-Butane was sensitizing the myocardium to epinephrine-induced cardiac arrhythmias in dogs after inhalation.

No reports on acute toxicity of n-butane in experimental animals by other administration routes were located in the available literature.

In a 21-day inhalation toxicity study of a mixture of n-butane, isobutane, n-pentane and isopentane, containing 25% of each, the absence of toxicity was evident up to 11.8 mg/l which was the highest concentration tested. The study was performed in Sprague-Dawley rats which were exposed 6 hours per day over three weeks for a total of 15 exposures. No long-term studies using pure n-butane were located in the available literature.

No mutagenic activity was observed in several tests in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 with or without the addition of an exogenous metabolism system.

No studies on carcinogenicity, reproduction toxicity and teratogenicity, immunotoxicity or allergy were located in the available literature.

Several reports on human exposure to n-butane were available. The increasing abuse of volatile substances, n-butane being among them, increases the risk of sudden death in connection to inhalation of the gas. The range of concentrations that may lead to "high" feelings or to death has been noted to be very narrow. The use of an oven cleaner containing n-butane as propellant has caused transient myoclonus in one patient. No other physical abnormalities were noted. An aerosol spray which contained n-butane as propellant, was reported to cause deep frostbite symptoms in the skin when sprayed directly on it.

Because of the anaesthetic effect of n-butane, truck drivers and terminal operators from different loading facilities and service stations were examined for exposure to gasoline vapours containing 90 to 92 percent n-butane, isobutane, n-pentane and isopentane. Exposures to the gasoline vapour were substantially lower than the established ACGIH threshold values (300 ppm or 0.89 mg/l for gasoline, and 800 ppm or 1.9 mg/l for n-butane).

Occupational exposure of 53 male refinery workers for an average of 11 years to n-butane (concentration varied from 0.0004 mg/l to 0.0178 mg/l) did not cause any clinical symptoms in the workers.

In some case reports symptoms in the central nervous system of n-butane abusers have been noted. Visual hallucinations, increasing irritability and tendency to become easily provoked, leading to social isolation, were some of the symptoms in a 16-year-old girl who had been inhaling n-butane for 1 year. In an other case report, a rapid and severe liver damage has been suggested to be the result of heavy and longstanding n-butane abuse in a 17-year-old male.

In conclusion, exposure to low concentrations of n-butane has not been reported to cause adverse effects in humans. It is anaesthetic to both humans and experimental animals. Sudden death may occur when n-butane is inhaled at high concentrations. The safety margin between anaesthetic and lethal concentrations appears to be very narrow. Chronic exposure to n-butane has been reported to cause some symptoms in the central nervous system. Critical effects might be lethality when inhaled in high doses, and effects on the central nervous system in chronically exposed individuals.

1. NAME, SYNONYMS AND TRADE NAMES

1.1	**Name:**	Butane	
1.2	**Synonyms:**	n-Butane, normal butane	(1)
1.3	**Trade names:**	none	

2. STRUCTURE AND IDENTITY

2.1	**CAS No:**	106-97-8
2.2	**EINECS No:**	203-448-7
2.3	**Molecular formula:**	C_4H_{10}
2.4	**Structural formula:**	

$$CH_3-CH_2-CH_2-CH_3$$

3. PHYSICAL AND CHEMICAL PROPERTIES

3.1	**Molecular weight:**	58.12	
3.2	**Melting point:**	-138 °C	(1, 2, 3)
3.3	**Boiling point:**	-0.5 °C	(1, 2, 3)
3.4	**Relative density:**	2.07 (air = 1)	(1, 3)
3.5	**Vapour pressure:**	2 670 mm Hg (356 kPa at 37.8 °C) 1 823 mm Hg (243 kPa at 25 °C) 760 mm Hg (101.3 kPa at 0 °C)	(4, 5)
3.6	**Solubility:**	61 mg/l in water at 20 °C; soluble in alcohol and ether	(1, 5)
3.7	**pH:**	not applicable	

3.8	**Partition coefficient:**	log K_{ow} = 2.89	(1)
3.9	**Description:**	colourless, flammable gas at room temperature	(3)
3.10	**Decomposition temp:**	no data were available	
3.11	**Flammability:**	-60 °C (closed cup)	(1, 2, 3)
3.12	**Explosivity:**	lower limit 1.9%, upper limit 8.5% by volume	(2)
3.13	**Oxidizing properties:**	no data were available	
3.14	**Conversion factor:**	1 ppm = 2.37 mg/m^3 1 mg/m^3 = 0.422 ppm	(1, 3)

4. PRODUCTION, PURITY, USE AND OCCURRENCE

4.1 Production

n-Butane is produced from natural gas and from petroleum products by catalytic cracking, and other refining processes. Liquid n-butane is recovered from the feedstock gas through a "debutanizing" process involving refrigeration, and other cryogenic steps (1).

4.2 Purity

The purity specification for "pure" n-butane is 99.9%, and for technical n-butane 95%. Technical n-butane may contain isobutane, isopentane, propane, n-pentane, cyclopentane, unsaturated hydrocarbons and sulphur compounds in trace amounts. The concentrations of isobutane and n-pentane may reach 4% and 2%, respectively (6).

4.3 Use

n-Butane is used in liquid fuels of high octane, in organic synthesis of different chemicals, in the production of synthetic rubbers, as a refrigerant and aerosol propellant, and as a constituent in liquid natural gas (1, 2).

4.4 Occurrence

n-Butane occurs in natural gas, and in small concentrations in the ambient community air originating from combustion of gasoline or similar petroleum products (3, 7).

5. TOXICOKINETICS

5.1 Absorption

Absorption of n-butane in humans has been reported to be 30 - 45% of the inhaled dose (8). No reports on absorption by other administration routes were located in the available literature.

5.2 Distribution

In post mortem examinations, unchanged n-butane was found in brain, liver, kidney, spleen and perinephric fat of rats and in brain of mouse after inhalation exposure (8, 9).

5.3 Metabolism

It has been reported that hydroxylation of n-butane occurs in rat liver microsomes yielding 2-butanol as the major metabolite. No detailed information has been available (1).

5.4 Excretion

n-Butane is largely excreted unchanged in exhaled air and in urine (8).

6. TOXICITY IN EXPERIMENTAL SYSTEMS

6.1 Acute toxicity

Acute toxicity of n-butane has been studied in rats and mice after inhalation exposure. In rats LC_{50}/ 4h was found to be 658 mg/l (278 000 ppm) and in mice LC_{50}/ 2h was 680 mg/l (287 000 ppm) (1, 9).

A few inhalation studies were performed in dogs in order to determine anaesthetic concentrations of n-butane. Concentrations of 200 000 to 250 000 ppm (474 to 592 mg/l) were required to produce relaxation in dogs, these concentrations produced also lethality in all dogs within a few minutes. No further details were reported (10). Only a small safety margin was between anaesthetic and lethal concentrations. In mice, inhalation exposure to 13% (308 mg/l) n-butane caused light anaesthesia within 25 minutes. When exposed to 22% (521 mg/l) n-butane, light anaesthesia was observed within 1 minute and complete anaesthesia within 15 minutes in mice (10).

Fifteen to 90% (355 - 2 133 mg/l) n-butane has been shown to sensitize the myocardium to epinephrine-induced cardiac arrhythmias in dogs during a 10-minute exposure (11). The heart was sensitized to epinephrine-induced ventricular fibrillation by 1 - 20% (24 - 474 mg/l) n-butane exposure for periods of 2 minutes to 2 hours in dogs (1, 12).

Increased respiratory rate, sniffing and chewing behaviour have been observed in guinea pigs exposed to 21 000 to 56 000 ppm (50 - 133 mg/l) of n-butane (1, 3).

No reports on acute toxicity of n-butane by other administration routes were located in the available literature.

6.2 Irritating and corrosive properties

No data on the irritating potential of n-butane were located in the available literature.

6.3 Subacute, subchronic and chronic toxicity

A 21-day inhalation toxicity study of a blend consisting of 25% (w/w) each of n-butane, isobutane, n-pentane and isopentane was conducted in rats to assess the potential of these major gasoline vapour components to induce kidney damage. The inhalation study consisted of four groups of rats (Sprague-Dawley, 10 males and 10 females per group), exposed to 0.12 mg/l (44 ppm), 1.15 mg/l (432 ppm), 11.80 mg/l (4 437 ppm) of the C_4/C_5 hydrocarbon blend, and to filtered air only. The rats were exposed to the test material 6 hours per day over three weeks for a total of 15 exposures. No treatment-related pathologic lesions either on gross- or microscopic examination were noted during the study. The absence of clinical signs of distress was evident up to 11.8 mg/l (4 437 ppm) of the hydrocarbon blend (13).

No long-term studies using pure n-butane were located in the available literature. The above study suggests that short term exposures to the four

major components of typical occupational gasoline vapour at concentrations that far exceed worst case work place conditions, produce no kidney damage in rats. Further studies are needed to evaluate toxic effects after long-term exposure to n-butane.

6.4 Carcinogenicity

No studies were located in the available literature.

6.5 Genotoxicity

The mutagenicity of n-butane has been tested in the Ames test using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 in the presence and absence of an exogenous metabolism system. The test substance was 99.7% pure n-butane containing 0.3% isobutane. It was tested at concentrations of 5, 10, 20, 30, 40 and 50% (the concentration of gas in the desiccator), and was not found to be mutagenic in any of the tested strains (14).

No mutagenic activity was found when n-butane was tested in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, and *Escherichia coli* strain WP2uvrA with and without an exogenous metabolism system. The substance was tested at concentrations of 0 to 10 000 ppm (23.7 mg/l) in the glass chamber (15).

The same strains of *Salmonella* were also used by the National Toxicity Program (NTP) of U.S. Department of Health and Human Services to examine the mutagenic potential of n-butane. No mutagenic activity was noted at doses of 0 to 10 000 µg/plate (NTP unpublished results). No further details were given.

n-Butane was also tested in the *Drosophila* sex-linked recessive lethal test. No mutagenic activity of n-butane was observed (NTP unpublished results). No further details were given.

6.6 Reproduction toxicity and teratogenicity

No data were available.

6.7 Immunotoxicity

6.7.1 *Allergy*

No data were available.

6.7.2 *Other immunotoxic effects*

No data were available.

6.8 Other toxic effects

No data were available.

7. HUMAN DATA

7.1 Acute toxicity

A case report on a female patient who suffered of transient myoclonus after exposure to a solvent-based oven cleaner has been located. She had sprayed the material four times a day during one day using 300 ml of the substance. The duration of each cleaning phase was up to 1.5 hours. She became progressively nauseated, anorexic and finally lightheaded. Fifteen to 20 minutes after finished work involuntary movements started in both shoulders spreading to the rest of the body. There were no other physical abnormalities on clinical examination. The symptoms were suggested to be caused by n-butane which was the propellant in the oven cleaner. It was not likely that the other ingredients, such as sodium hydroxide and detergents, were responsible for the effects (16).

Ventricular tachycardia was observed in a 2-year-old girl after playing with an aerosol can of a deodorant. The propellants used in this product were n-butane, isobutane and propane. No further reports on human cardiotoxicity have been available, but the animal evidence indicate a cardiotoxic potential of the substance (17).

The increasing abuse of volatile substances by inhalation gives rise to several reports of chronic toxicity. The concentration range when causing excitement and lethality is very narrow. n-Butane has caused sudden death when inhaled. A case report describes an 11-year-old boy who had been sniffing n-butane gas from a cigarette-lighter. In a post mortem examination no evidence of organic disease or anatomical causes of death were found (18).

7.2 Irritating and corrosive properties

Due to the low boiling point of n-propane (- 42.2 °C) and n-butane

(- 0.5 °C) a deep frostbite will occur if a propellant containing the mixture is sprayed on the skin. A case report describes a nonpainful, swollen, erythematous lesion which extended to the epidermis in an 8.5-year-old boy after playing with an aerosol containing n-propane and n-butane as propellants. He had sprayed his arm with a toilet air freshener at close range for an unknown length of time (19).

7.3 Chronic toxicity

The chronic exposure to gasoline vapour was studied on truck drivers and terminal operators from five loading facilities, on dockmen and seamen at two tanker/barge loading facilities and on attendants at a single expressway service station. Terminal and marine loading exposures revealed that four C4/C5 vapour components, n-butane, isobutane, n-pentane and isopentane, comprised approximately 90 to 92% of all the C4/C5 vapour components and approximately 61 to 67% of the total gasoline samples.The measured concentrations ranged from 0.04 to 0.09 mg/l at terminals, the highest measured value was 0.246 mg/l at marine loading facilities. Exposures to the gasoline vapour were substantially below the established ACGIH-TLV (300 ppm or 0.89 mg/l for gasoline; 800 ppm or 1.9 mg/l for n-butane) (2, 20).

Fifty-three male oil refinery workers were examined for kidney function and damage following exposure to n-butane using sensitive biochemical and immunological markers. The mean duration of exposure was 11 years, and the level of it was below the current threshold limit values. The studied parameters were ß-N-acetyl-D-glucosaminidase, $ß_2$-microglobulin and retinol-binding protein. No differences were found between the exposed individuals and age- and sex-matched control persons. The levels of circulating immune complexes were also identical in both groups. It could be concluded that the chronic low-level hydrocarbon exposure in these refinery workers did not induce clinically significant renal abnormalities. The mean concentration of n-butane varied from 0.0004 mg/l (refinery operator, onsite) to 0.0178 mg/l (gasoline truck driver) (21).

n-Butane abuse is a common phenomenon predominantly among males between 8 and 19 years of age. Chronic toxicity is difficult to assess. However, it is clear that some long-term abusers suffer permanent damage to the central nervous system, heart, liver and kidney (22).

A case report describes a 16-year-old girl who had been inhaling n-butane for a year. During the previous 3 months she had inhaled a total quantity of 5 litres of n-butane. During the period of abuse, she initially suffered from visual hallucinations, her school attendance became very irregular, a gradual deterioration in social functioning was leading to social isolation, and she was becoming increasingly irritable and easily provocative. No signs of toxicological symptoms were observed at the physical examination. The

patient did not cooperate with further haematological and physiological investigations (23).

Death due to fulminant hepatic failure following solvent abuse was reported (24). A 17-year-old male with a history of n-butane aerosol abusing (5 to 10 cans per day) for 3 years was admitted to surgical ward because of abdominal pain and vomiting. He developed hepatomegaly, polyuria and jaundice and died. Post mortem examination showed cerebral oedema, and extensive necrosis of the liver. The symptoms occurred after he was taking a proprietary engine or carburettor cleaner which did not contain n-butane. The longstanding and heavy abuse of n-butane may have resulted in microsomal enzyme induction and thus, could have been an important factor in the rapid and severe nature of liver damage.

The increased incidence of aerosol abuse has led to development of a method for detection of halogenated hydrocarbons in the body fluids and tissues. n-Butane is often used in propellants in combination with halogenated hydrocarbons such as freons. Using headspace desorption gas chromatography - mass spectrophotometry for sampling, the separation and identification of the freons and other hydrocarbons has became unequivocal. A case report described a 16-year-old girl found dead in a bathroom with a Bodymist 2 aerosol can deodorant floating in the water. Three propellant materials were detected in the aerosol can: Freon 12, n-butane and Freon 11. In the patient's blood sample, n-butane and Freon 11 were detected (25).

7.4 Other toxic effects

No data were available.

8. DISCUSSION

n-Butane is a colourless and flammable gas at room temperature. It is produced from natural gas and petroleum products by cracking and other refining processes. It is used in fuels, in organic syntheses, as refrigerant and aerosol propellant. n-Butane occurs most often in a mixture together with isobutane, n-pentane and n-propane.

In metabolism studies in rat, n-butane has been shown to be metabolized by liver microsomes to 2-butanol. No further metabolic studies have been located. In post mortem examinations following n-butane exposure, the substance has been found in brain, liver, kidney, spleen and perinephric fat of rats and in

brain of mice. In both rats and mice, the brain concentrations of n-butane correlated with the degree of CNS depression and narcosis.

The acute toxicity of n-butane has been studied in experimental animals after inhalation exposure. In rats, LC_{50} (4h) was 658 mg/l (278 000 ppm) and in mice, LC_{50} (2h) was 680 mg/l (287 000 ppm). In dogs, n-butane was lethal at 200 000 to 250 000 ppm (474 to 592 mg/l). Lethality has also been reported in humans following abuse by inhalation of high concentrations of n-butane. The gas concentration that has anaesthetic and relaxing effects has been shown to often be very close to the lethal concentration in experimental animals. n-Butane has also been shown to have cardiotoxic and neurotoxic potential in experimental animals. It has been shown to sensitize the heart to epinephrine-induced ventricular fibrillation and cardiac arrhythmias in dogs. In guinea pigs increased respiratory rate, sniffing and chewing behaviour was observed after exposure to 21 000 - 56 000 ppm (50 - 133 mg/l).

Some cases of sudden death in connection with n-butane inhalation abuse have been reported. n-Butane was suggested to cause transient myoclonus in one patient and cardiac toxicity symptoms in another patient following the use of an aerosol can containing n-butane as propellant.

No reports on skin or eye irritation by n-butane gas have been located. Liquid n-butane gas has been reported to cause severe frostbite when sprayed onto the skin. The frostbite depends on the low boiling point of the gas, cooling the skin rapidly when evaporating from the skin.

In chronic toxicity testing no clinical signs of distress or pathologic lesions were noted in rats during a 21-day inhalation study with up to 11.8 mg/l of a C4/C5 hydrocarbon blend containing 25% ($^{w}/_{w}$) each of n-butane, isobutane, n-pentane and isopentane. Epidemiological studies have been performed on truck drivers and terminal operators from different loading facilities and refinery workers. In these occupational environments the concentration of the gas was below the established ACGIH-TLV (300 ppm or 0.89 mg/l for gasoline, and 800 ppm or 1.9 mg/l for n-butane). No clinical symptom were observed in the workers who had been exposed for 11 years on the average.

In humans, it has been difficult to measure tissue concentrations of n-butane after exposure. The increased incidence of aerosol abuse has, however, led to successful development of a gas chromatographic method to detect trace amounts of n-butane and halogenated hydrocarbons in the body fluids and tissues.

Increasing abuse of volatile substances, n-butane being among them, has been reported to cause different problems predominantly among males between 8 and 19 years of age (22, 23). Some long-term abusers suffer from irritation, hallucinations and other symptoms of the toxic effect of n-butane on the central nervous system. Permanent damage to heart, liver and kidney tissues was also observed in the postmortem examination of some n-butane abusers.

n-Butane did not show any mutagenic activity when tested in the Ames test or in *Escherichia coli* strain WP2uvrA in the presence and absence of an exogenous metabolism system. No further studies on the genotoxicity of n-butane were available.

No reports concerning acute toxicity by other administration routes than inhalation, long-term toxicity, carcinogenicity, immunotoxicity or reproduction toxicity have been located in the available literature.

In conclusion, n-butane is a gas which has low acute inhalation toxicity to experimental animals and humans at moderate concentrations. Chronic exposure to n-butane causes symptoms in the central nervous system and repeated exposure by inhalation to high concentrations of n-butane has caused sudden death in exposed individuals. Acute inhalation of high concentrations of n-butane has also caused cardiotoxic symptoms in experimental animals.

9. REFERENCES

1. Low, K.L., Meeks, J.R., Mackerer, C.R. n-Butane. In: Snyder, R. (ed.) *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, 2nd ed., Vol. 1: Hydrocarbons, pp. 267-272. Elsevier Science Publishers, B.V., Amsterdam, 1987.

2. *ACGIH*, American Conference of Governmental Industrial Hygienists Inc. Threshold limit values and biological exposure indices. 6th edn. Cincinnati, Ohio, 1991.

3. Sandmeyer, E.E. Aliphatic hydrocarbons. In: Clayton, G.D. and Clayton, F.E. (eds.) *Patty's Industrial Hygiene and Toxicology*, 3rd ed., John Wiley & Sons Inc., New York, 1978.

4. Beilstein Online, Springer Verlag, 1994.

5. Windholz, M., Budavar, S., Blumetti, R., Otterbein, E. (eds) *The Merck Index*. An Encyclopedia of Chemicals and Drugs. 10th ed. Merck and Co., Inc., Rahway, N.J., USA, 1983.

6. Boesiger, D.D., Nielsen, R.H., Albright, M.A. Butanes. In: Grayson, M, and Eckroth, D. (eds.) *Kirk-Othmer, Encyclopedia of chemical technology,* Vol. 12, pp. 910-919, 3rd ed., John Wiley & Sons, New York, 1980.

7. Chan, C.-C., Özkaynak, H., Spengler, J.D., Sheldon, L. Driver exposure to volatile organic compounds, CO, Ozone, and NO_2 under different driving conditions. Environ Sci Technol **25**, 964-972, 1991.

8. Flanagan, R.J., Ruprah, M., Meredith, T.J., Ramsey, J.D. An introduction to the clinical toxicology of volatile substances. Drug Saf **5**, 359-383, 1990.

9. Shugaev, B.B. Concentrations of hydrocarbons in tissues as a measure of toxicity. Arch Environ Health **18**, 878-882, 1969.

10. Stoughton, R.W., Lamson, P.D. The relative anaesthetic activity of the butanes and pentanes. J Pharmacol Exp Ther **58**, 74-77, 1936.

11. Krantz Jr, J.C., Carr, C.J., Vitcha, J.F. Anesthesia XXXI. A study of cyclic and noncyclic hydrocarbons on cardiac automaticity. J Pharmacol Exp Ther **94**, 315-318, 1948.

12. Glenoweth, M.B. Ventricular fibrillation induced by hydrocarbons and epinephrine. J Ind Hyg Toxicol **28**, 151-158, 1946.

13. Halder, C.A., van Gorp, G.S., Hatoum, N.S., Warne, T.M. Gasoline vapor exposures. Part II. Evaluation of the nephrotoxicity of the major C_4/C_5 hydrocarbon components. Am Ind Hyg Assoc J **47**, 173-175, 1986.

14. Kirwin, C.J., Thomas, W.C., Simmon, V.F. In vitro microbiological mutagenicity studies of hydrocarbon propellants. J Soc Cosmet Chem **31**, 367-370, 1980.

15. Shimizu, H., Suzuki, Y., Takemura, N., Goto, S., Matsushita, H. The results of microbial mutation test for forty-three industrial chemicals. Jpn J Ind Health **27**, 400-415, 1985.

16. Peatfield, R.C., Boothman, B.R. Transient myoclonus after exposure to oven cleaner. Mov Disord **6**, 90-91, 1991.

17. Wason, S., Gibler, B., Hassan, M. Ventricular tachycardia associated with non-freon aerosol propellants. JAMA **256**, 78-80, 1986

18. Siegel E, Wason, S: Sudden death caused by inhalation of butane and propane. N Eng J Med **323**, 1638, 1990.

19. Lacour, M., Le Coultre, C. Spray-induced frostbite in a child: A new hazard with novel aerosol propellants. Pediatr Dermatol **8**, 207-209, 1991.

20. Halder, C.A., van Gorp, G.S., Hatoum, N.S, Warne, T.M. Gasoline vapour exposures. Part I. Characterization of workplace exposures. Am Ind Hyg Assoc J **47**, 164-172, 1986.

21. Viau, C., Bernard, A., Lauwerys, R., Buchet, J.P., Quaeghebeur, L., Cornu, M.E., Phillips, S.C., Mutti, A., Lucertini, S., Franchini, I. A gross-sectional survey of kidney function in refinery employees. Am J Ind Med **11**, 177-187, 1987.

22. Ramsey, J., Anderson, H.R., Bloor, K., Flanagan, R.J. An introduction to the practice, prevalence and chemical toxicology of volatile substance abuse. Hum Toxicol **8**, 261-269, 1989.

23. Mathew, B., Kapp, E., Jones, T. R. Commercial butane abuse: a disturbing case. Br J Addict **84**, 563-564, 1989.

24. McIntyre, A.S., Long, R.G. Fatal fulminant hepatic failure in a 'solvent abuser'. Postgrad Med J **68**, 29-30, 1992.

25. Hamill, J., Kee, T.G. The detection of aerosol propellants in body fluids and tissue by gas chromatography-mass spectrometry. J Forensic Sci Soc **31**, 301-307, 1991.

Human Toxicol. (1982), 1, 239–247

文献 11

Acute Inhalation Toxicity of Some Halogenated and Non-halogenated Hydrocarbons

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1 The relative potency of effect of a wide range of halogenated and unsubstituted hydrocarbons on the central nervous system (CNS) and the heart of experimental animals have been determined.

2 The chemicals used caused either stimulation or depression of the rat CNS after 10 minutes' inhalation of concentrations ranging from 0.24% to > 80% (v/v), and cardiac sensitization in dogs after 5 minutes' inhalation of 0.12% to approximately 80% (v/v).

3 The toxicity could not be correlated with chemical structure, molecular weight, the presence or absence of various halogen atoms or the degree of saturation, but it was inversely related to the saturated vapour pressure. When the results were expressed on a thermodynamic scale the chemicals had similar potencies at relative saturations of 0.004 to 0.04

4 It is suggested that the effects of these chemicals on the CNS and the heart are probably structurally non-specific, and the chemicals may be regarded as physical toxicants whose effects are predictable from their physico-chemical properties.

Introduction

Halogenated and unsubstituted hydrocarbons have been widely used for many years as solvents, aerosol propellants, fire extinguishants and refrigerants. The toxic effects of many of these chemicals following short periods of exposure by inhalation have been well documented as narcosis leading to death from profound respiratory depression. (Robbins, 1946; Krantz & Rudo, 1966).

Death can also occur following sensitization of the heart to the arrhythmogenic actions of adrenaline. Several cases of sudden death have been reported during industrial use of some of these chemicals (Reinhardt *et al.*, 1971), and sudden death amongst teenagers inhaling them for mood enhancement has been attributed to ventricular fibrillation following cardiac sensitization (Reinhardt *et al.*, 1971). Although many chemicals have been abused by inhalation (Table 1), comparison of their potencies on the central nervous system (CNS) and the heart is difficult since most published toxicity data have been developed under different

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0144-5952/82/030239-09 $01.00

Table 1 Some of the chemicals abused by inhalation

Chemical	*Industrial use*
Toluene Acetone Hexane Ethyl acetate Methyl ethyl ketone	Adhesives
FC 11 FC 12 Methylene chloride Isobutane Propane	Aerosols
Chloroform Trichloroethylene Carbon tetrachloride Trichloroethane FC 113 Hexane	Solvents
Carbon tetrachloride FC 13 B1 BCF FC 114 B2	Fire extinguishants

experimental conditions. The present work therefore investigates the relative concentrations at which CNS and cardiac effects occur under standard experimental conditions.

Methods

Chemicals

The chemicals were either supplied by Imperial Chemical Industries, PLC, Mond Division, to commercial specification or were standard AR grade laboratory chemicals. Gases were supplied in pressurized cylinders; liquids in tins or bottles.

The fluorinated chemicals are named in two ways: by their chemical name and by the numerical system described by Hamilton (1963). The following descriptions were used: Difluorotetrachloroethane (FC 112); dibromotetrafluoroethane (FC 114B2); trifluorotrichloroethane (FC 113); trichlorofluoromethane (FC 11); bromochlorodifluoromethane (BCF); difluorodichloromethane (FC 12); difluorochloromethane (FC 22); trifluorobromomethane (FC 13B1); trifluorochloromethane (FC 13).

Generation of atmospheres

Chemicals that were gaseous at room temperature were simply passed through a calibrated rotameter, mixed with the required amount of air and the resulting atmosphere was passed to the animal model. The rotameters were initially calibrated by a wet test meter. Chemicals that were liquid at room temperature were vaporized either by using an anaesthetic dispenser, calibrated for each chemical, or by passsing air through the liquid and making appropriate dilutions with air. For fluorocarbon 11 a syringe and atomizer technique (Gage, 1959) was used with the apparatus maintained in ice. The resulting micro-aerosol was passed into a warmed mixing chamber where it was mixed with air and passed to the animal model.

Dynamic atmospheres were generated in each case and the concentration of the chemical in the atmosphere was measured by gas chromatography. Oxygen was mixed with the air to maintain a concentration of 20% oxygen as soon as the atmospheric concentration of the chemical under test exceeded 25%.

Estimation of LC_{50}, EC_{50} (CNS) and EC_{50} (CS)

Specific pathogen-free rats of the Alderley Park strain with body weights ranging from 190–230 g were used. Groups of six male or female animals were exposed to the chemicals in a 500 ml chamber through which the vapours, mixed with air, were passed. The animals were observed for effects on the central nervous system, either stimulation (tremors of the limbs) or depression (ataxia and loss of righting reflex), over a 10 min exposure period. A range of concentrations was used such that the no-effect concentration, the 100% effect concentration and several in-between concentrations were determined. The EC_{50} CNS effect concentration (10 min) was then calculated.

The concentrations causing death after 15 min exposure were also determined and the LC_{50} (15 min) was calculated.

The EC_{50} for cardiac sensitization to adrenaline in dogs after 5 min exposure was determined as described previously (Beck, Clark & Tinston, 1973).

Statistics

The EC_{50}, LC_{50} and 95% confidence intervals were calculated using the moving average interpolation technique of Thompson (1947).

Results

The results of the EC_{50} (CNS effects) and LC_{50} determinations in rats are presented in Table 2, divided into CNS depressants or stimulants on the basis of the clinical signs of toxicity. Death following exposure to a CNS depressant took the following form: slight ataxia, loss of righting reflex, loss of movement, narcosis, shallow respiration and death eventually from respiratory depression.