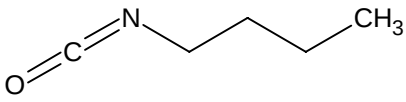
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-36-4
Chemical Name	n-Butyl isocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

n-Butyl isocyanate is a liquid with a high vapor pressure under ambient conditions, therefore the primary route of potential human exposure is inhalation (vapor saturation concentration (20 °C) = 81,546 mg/m³). Thus, the most relevant route of exposure for toxicity testing is via inhalation. In general, the toxicological effects observed resulting from inhalation exposure reveal a pattern characteristic of acute irritation and its sequealae. This mode of action for this class of compounds is wholly consistent with the chemical reactivity of the isocyanate functional group. Isocyanates will seek nucleophiles at the point of deposition, and the lung contains a relatively high level of non-protein sulfhydryls such as glutathione as well as proteins with accessible –SH, -OH, -NH and –COOH groups for interaction with isocyanate functional group. With this understanding of toxicological mode of action it is feasible that if the exposure concentration of n-butyl isocyanate is held below the threshold for respiratory tract irritation it is not expected that any systemic toxic effects would occur.

There are no reproductive, developmental, or *in vivo* genetic toxicity studies available for n-butyl isocyanate. However, since inhaled n-butyl isocyanate vapor would react primarily with lung tissue conducting studies to evaluate toxicity to systemic organ systems is not expected to yield useful information in assessing the human health hazard of n-butyl isocyanate. Any observed systemic effects may be secondary to direct effects on the respiratory tract.

No studies were found that presented data on toxicokinetics, metabolism and distribution.

After inhalation of isocyanate vapor, amine formation in the respiratory tract, if it occurs, is not expected to play a significant role rather the reactivity of the isocyanate group with nucleophilic groups located on the surfaces of the respiratory tract dominates. On the other hand, amine may occur to a significant extent after oral administration, i.e. in the acidic conditions prevalent in the stomach. The oral LD_{50} was determined to be 360 mg/kg bw for rats. Toxic symptoms included apathy, stiff gait, and labored breathings. Acute inhalation toxicity studies revealed that n-butyl isocyanate is highly toxic when inhaled. The LC_{50} (rat, 4h) value reported in a study according to OECD TG 403 with vapor inhalation is 59 mg/m³. Assessment of the acute inhalation toxicity data indicates that the primary toxic effects in response to exposure to evaporated n-butyl isocyanate are focused on the portal of entry, the respiratory tract. Thus death is due to severe respiratory tract lesions. Special investigations with male rats revealed overt inflammatory responses in the lung, which also could be confirmed histopathologically. The prominent microscopic changes were increased number of macrophages, perivascular round-cell infiltration, focal fibroproliferative reactions, emphysema, thickening septa, and abscessive pneumonia. Inflammation of the airways became prominent after exposure of a lethal concentration (50 mg/m³, 1x4h) and was marginally pronounced at a sublethal concentration (25 mg/m³, 1x4h)). No significant changes other than transient clinical signs were observed at 8 mg/m³. Ca. 3 mg/m³ were tolerated without any symptoms.

n-Butyl isocyanate is corrosive to skin and eyes of rabbits. The toxicity studies and one case report indicate that n-

butyl isocyanate vapor causes irritation of the respiratory tract. RD_{50} values for rat and mice of 40.4 mg/m^3 and 38.9 mg/m^3, respectively, were determined and gave evidence for a moderate sensory irritation potential of n-butyl isocyanate. 1 mg/m³ (RD_{50} x 0.03) was regarded as the threshold for sensory irritation in humans. One study with guinea pigs provides evidence of a skin sensitizing potential of n-butyl isocyanate. No validated data regarding respiratory sensitization is available. Due to the well known reactivity of isocyanates respiratory sensitization is likely to occur.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. No subacute inhalation study according to OECD TG 412 is available. An exploratory subacute vapor inhalation study (1, 5, 15, 25 mg/m^3, 5 x 6 hours/day) with male rats demonstrated obstructive and progressive lung disease (emphysema) at 25 mg/m³, which is considered to be the cause of delayed mortality. Repeated exposure of sublethal concentrations (≤ 15 mg/m³) did not lead to microscopic detectable adverse effects on the lung. Based on cageside observations and hypothermia a concentration of 5 mg/m³ was tolerated without toxicologically significant effects. But changes in biochemical and cellular components in bronchoalveolar lavage fluid (BALF) gave evidence for inflammations of the airways at n-butyl isocyanate concentrations ≥ 5 mg/m³. Thus the reported NOAEL is 1 mg/m^3; the LOAEL being 5 mg/m^3 which may be in excess of what is likely to be determined after inhalation during 28 days.

n-Butyl isocyanate did not induce gene mutations in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100 with and without metabolic activation up to 5000 µg/plate (OECD TG 471, 1983). The substance was genotoxic in the mouse lymphoma assay only in absence of a metabolic activation system. No differentiation between small and large colony mutants was performed in this test and therefore it cannot be concluded whether the positive result is attributable to gene mutations or chromosomal aberrations. However, the structural analogue methyl isocyanate is not mutagenic in bacteria, but gives consistently positive results in tests indicative for chromosomal aberrations *in vitro*. Therefore it is expected that the positive result in the mouse lymphoma assay with n-butyl isocyanate is based on chromosomal aberration. There are no genotoxicity studies *in vivo* available. Overall n-butyl isocyanate showed genotoxic potential *in vitro* and it is anticipated that it has the potential to be genotoxic *in vivo*.

There are no reproductive or developmental toxicity studies of n-butyl isocyanate available. No information with regard to reproductive organs is given in the 5-days inhalation study. Since inhaled n-butyl isocyanate vapor will react primarily with lung tissue so that other systemic organ systems or tissues would be affected only at exposure concentrations that produce sufficient lung toxicity. But the propensity of n-butyl isocyanate to cause lung effects consequently led to secondary effects such as hypoxia that could influence developmental endpoints. Therefore it is not expected to yield useful information from a reproductive or developmental toxicity study of n-butyl isocyanate vapor inhalation. Thus reproductive toxicity cannot be excluded, but it seems to be unlikely at non irritant n-butyl isocyanate exposure concentrations.

Environment

n-Butyl isocyanate is a colorless to yellowish, moisture/water sensitive liquid with a melting point of –75 °C and a boiling point of 116 °C at 1013 hPa. n-Butyl isocyanate has a relative density of 0.88 g/cm^3 at 20 °C and a vapor pressure of ca. 25 hPa at 21 °C. Measurements or calculations of water solubility for a substance rapidly hydrolyzing in water are not suitable. The flash point is 19 °C (closed cup), the ignition temperature is 425 °C, and the viscosity is 0.04973 Pa at 20 °C. n-Butyl isocyanate is highly flammable. n-Butyl isocyanate hydrolyzes completely in water within a few minutes at 20 °C, forming n-butylamine.
The most important values of the degradation product n-butylamine (neutral form) concerning environmental behavior and ecotoxicology are a melting point of –50 °C, a vapor pressure of 127hPa at 25 °C, a log K_{OW} of 0.97, and a water solubility of 202900 mg/l at 25 °C.
In the atmosphere n-butyl isocyanate is degraded by photochemically produced OH radicals. The half-life is calculated to be about 4 days. For n-butylamine a half-life of 0.5 days is estimated.
A DT_{90}< 1 d was determined for n-butyl isocyanate in four different kinds of soil under different moisture and texture characteristics as well as different organic carbon content and pH conditions. After 4 days n-butyl isocyanate was completely removed. n-Butyl isocyanate and its degradation product n-butylamine are readily biodegradable. In an aquatic test on aerobic ready biodegradability conducted comparable to OECD TG 301D, 62 % biodegradation related

to ThOD was reported after 20 days for n-butyl isocyanate. For its degradation product, n-butylamine, 85 % biodegradation was observed after 14 days in a test system comparable to OECD TG 301C.

Due to the rapid hydrolysis of n-butyl isocyanate in water, the distribution of the hydrolysis product n-butylamine is calculated. With a pK_a of 10.77 at 20 °C, n-butylamine will exist predominantly in its protonated form in the environment. According to the Mackay fugacity model level I, the favorite target compartment of the protonated form of n-butylamine is water with 99.99 %.
The calculated Henry's Law constant for n-butyl isocyanate is 220 Pa m³/mol at 25 °C proving a high potential for volatilization from surface waters. Since n-butyl isocyanate hydrolyses rapidly in water, volatilization will not be an important fate process. Regarding the Henry's Law constant of 1.66×10^{-7} Pa m³/mole for the protonated form of n-butylamine, the substance is not expected to volatilize from water.
The bioconcentration factors (BCF) of 11 for n-butyl isocyanate and 3.2 for n-butylamine, calculated from the octanol-water partition coefficients as well as the measured BCF of 4.1 for n-butylamine in eggs of *Danio rerio* indicate that there is a low potential for bioaccumulation of n-butyl isocyanate and n-butylamine in aquatic organisms.
K_{OC} values were calculated with PCKOCWIN v. 1.66 (K_{OC} = 275 for n-butyl isocyanate, K_{OC} = 61 for n-butylamine, K_{OC} = 112 for n-butylammonium chloride). In addition, experimentally obtained adsorption coefficients (K_{OC}) revealed a low sorption potential of n-butylamine. The experimentally achieved K_{OC} values were in the range of 15 to 107 depending on soil properties. These results indicate a low sorption potential of n-butyl isocyanate and n-butylamine onto the organic phase of soils or sediments.

Concerning the toxicity of n-butyl isocyanate and its hydrolysis product n-butylamine towards aquatic species and bacteria, there are tests available with n-butylamine and these can be used to interpret the expected effects of n-butyl isocyanate. The lowest reliable effect values for aquatic species (based on nominal concentrations) with n-butylamine towards fish, *Daphnia*, and algae are:

Menidia beryllina:	96 h-LC_{50} = 24 mg/l
Daphnia magna:	24 h-EC_{50} = 43 mg/l
Microcystis aeruginosa:	8 d-EC_{50} > 0.14 mg/l (biomass at test end)
	(This test measured an EC_3 with a non standard organism.)

Based on a QSAR estimation with ECOSAR (aliphatic amines) for n-butylamine an EC_{50} = 9.0 mg/l (96 h) is calculated for green algae.
For bacteria the lowest available toxicity value determined was a 16 h-EC_3 of 65 mg/l (*Pseudomonas putida*). For protozoa a 72 h-EC_5 of 8.8 mg/l (*Entosiphon sulcatum*) was determined. These effect values for microorganisms refer to nominal concentrations of n-butylamine, although toxicity data referring to n-butyl isocyanate are available, but in higher values.
Since there are acute test results available for the hydrolysis product n-butylamine, an assessment factor of 1000 was applied using the lowest available effect concentration (8 d-EC_{50} of > 0.14 mg/l) which was obtained for *Microcystis aeruginosa.* Calculation yielded a $PNEC_{aqua}$ > 0.14 µg/l. The expression of this value indicates the lowest toxicity threshold only. In this case, it will be appropriate to give the $PNEC_{aqua}$ as a range. Regarding the lowest effect concentration of the other trophic levels, the lowest value for fish (*Menidia beryllina*) of 24 mg/l by applying an assessment factor of 1000, is taken into account. Thus, the $PNEC_{aqua}$ is predicted to be $PNEC_{aqua}$ > 0.14 µg/l < 24 µg/l. (Using the ECOSAR result the PNEC is 9.0 µg/l.)

Exposure

n-Butyl isocyanate is predominantly produced by reaction of phosgene with n-butylamine. The only EU production site is located in Germany, with an annual manufacturing volume of 1000 - 5000 metric tonnes, which is sold to customers world wide. Small quantities of n-butyl isocyanate are assumed to be manufactured in China. The global production volume of n-butyl isocyanate is estimated to be about 1000 - 5000 metric tonnes in 2004.

n-Butyl isocyanate is exclusively used as an intermediate in chemical processes, mainly in the synthesis of carbamate and urea insecticides and of fungicides, and to a small extent, for sulfonyl urea antidiabetic drugs and as a catalyst in the chemical industry. A direct use of n-butyl isocyanate is not known. Virtually all of the n-butyl isocyanate is converted into two fungicides: IPBC (3-Iodo-2-propynyl-butyl-carbamate, CAS 55406-53-6) and benomyl (1-

(butylcarbamoyl)-2-benzimidazol-methylcarbamate, CAS 17804-35-2), which is not permitted for use in the USA and in the EU (with the exception of Slovakia).

n-Butyl isocyanate is confidentially listed in the Danish Product Register as a product for industrial use in 2000, 2001, and 2002 (last years of record). It is not listed in the Finnish, Norwegian, Swedish and Swiss Product Registers. The main use category is "use in closed system".
From the manufacturing site of the Sponsor country virtually no n-butyl isocyanate (< 25 kg) was emitted into the environment in 2003. With a detection limit of 7 µg/l the hydrolysis product n-butylamine was not detectable in the effluent of the manufacturer´s wastewater treatment plant. Due to the high vapor pressure of the substance, the most likely route of occupational exposure to n-butyl isocyanate is through inhalation. Dermal or oral exposure is unlikely to occur. At the manufacturer in the Sponsor country, exposure is controlled in occupational settings.
Pyrolytic n-butyl isocyanate was detected in smoke of building fires. Traces of pyrolytic n-butyl isocyanate were reported from smoked food and detected in the volatile flavor of fried bacon.
Overall, the exposure of consumers to n-butyl isocyanate is negligible.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (highly toxic to lung when inhaled, corrosive to skin and eye, moderately irritating to respiratory system, sensitization of skin and predicted to be a respiratory tract sensitizer because it is an isocyanate, potential for genotoxicity). Based on the data presented by the Sponsor country, exposure of workers in manufacturing in the only producer in the Sponsor country and of consumers is anticipated to be negligible. As no worker exposure data except from the producer in the Sponsor country is available, it is recommended to conduct an exposure and if indicated a risk assessment at the workplace apart from the production site. The chemical is a candidate for further work.

There are no reproductive, developmental, or *in vivo* genetic toxicity studies available for n-butyl isocyanate and the repeated dose study is limited to a 5 day exposure period with a major in lung toxicity. Because of the propensity for n-butyl isocyanate to produce portal-of-entry effects inhaled n-butyl isocyanate vapor would react primarily with lung tissue. Any observed systemic effects at irritant exposure concentrations may be secondary to direct effects on the respiratory tract. Furthermore, there is no evidence from acute and repeated exposure studies for "cumulative-dose" toxicity associated with n-butyl isocyanate. Thus conducting studies to evaluate toxicity to systemic organ systems is not expected to yield useful information in assessing the human health hazard of n-butyl isocyanate. Therefore for the purposes of satisfying SIDS testing requirements for hazard assessment it is concluded that no additional toxicity testing is necessary.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for 100 % of OECD production and relating to the use pattern in several OECD countries), emissions to the environment are anticipated to be low. Therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.