SCOEL/SUM/75
February 2007

Recommendation from the Scientific Committee

on Occupational Exposure Limits:

Risk assessment for 1,3-butadiene

Estimates on EXCESS DEATHS and SMR based on risk assessment													
TWA (ppm)													
0,1		**0,2**		**0,5**		**1**		**2**		**5**		**10**	
EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR
-1,02	**0,80**	**-1,02**	**0,80**	**-1,02**	**0,80**	**-0,09**	**0,98**	**-0,47**	**0,91**	**-0,05**	**0,99**	**1,73**	**1,34**
7,64	**2,50**	**7,64**	**2,50**	**7,64**	**2,50**	**10,78**	**3,12**	**9,88**	**2,94**	**11,67**	**3,30**	**21,45**	**5,26**

(Explanation in the text)

SUBSTANCE:

1,3-butadiene $CH_2=CH-CH=CH_2$

Synonyms : buta-1,3-diene; diethylene; divinyl; vinylethylene.

EINECS No : 203-450-8

EEC No : 601-013-00-X

Classification : F+: R 12; Carc Cat. 1: R45; Muta. Cat 2: R46

CAS No : 106-99-0

MWt : 54.09

Conversion factor (20°C, 101 kPa) : 2.25 mg/m^3 = 1 ppm

OCCURRENCE/USE:

1,3-butadiene is a colourless gas with a mild aromatic or gasoline-like odour. It has an MPt of -109°C, a BPt of -4.4°C and a vapour pressure of 248 kPa at 20°C. The vapour density is 1.9 times that of air, and it is explosive in the range 2.0% - 11.5 % in air. The odour threshold is about 2 ppm (approx. 4 mg/m^3).

Butadiene is a highly reactive material which can polymerise readily, particularly in the presence of oxygen. The principal uses of 1,3-butadiene are in the manufacture of synthetic rubber such as styrene-butadiene rubber (SBR) or polybutadiene rubber used in tyres and tyre products, thermoplastic resins used in automotive parts and business machines, and styrene-butadiene latex suspensions used in paints and carpet backings. It is also used as a chemical intermediate in the production of neoprene and adiponitrile. Butadiene is a major commodity chemical of the petrochemical industry with a production level within the EU in excess of one million tonnes per annum.

HEALTH SIGNIFICANCE:

The main documentation used by the SCOEL in the evaluation of butadiene was a criteria document prepared by ECETOC (1997).

Butadiene is well-absorbed through the lungs and distributed widely in the body. Metabolic elimination of butadiene is linearly related to ambient exposure concentration up to about 1000 ppm (2250 mg/m^3) in rats and mice, with mice showing higher elimination rates. The metabolic pathways appear to be saturated above 1000 ppm (2250 mg/m^3) in rats and mice and above 300 ppm (675 mg/m^3) in monkeys (Kreiling *et al*., 1986, 1987; Sabourin *et al*., 1992). Butadiene is rapidly metabolised by cytochrome P450-dependent mono-oxygenases to 1,2-epoxy-3-butene, which is further metabolised by three pathways: (i) hydrolysis by epoxide hydrolases to 3-butene-1,2-diol (ii) further epoxidation to 1,2,3,4-diepoxybutane, and (iii) conjugation with glutathione (Malvoisin *et al*., 1979; Malvoisin and Roberfroid, 1982). According to both *in vitro* and *in vivo* data, the biotransformation appears to be qualitatively similar across species, including humans (Kreuzer *et al*., 1991; Csanády *et al*., 1992; Sabourin *et al*., 1992). However, because of differences in uptake and kinetics, the steady-state blood and tissues levels are quantitatively different. The body burden for 1,2-epoxy-3-butene appears to be up to three times higher for mice than for rats (Kreiling *et al*., 1986, 1987; Bond *et al*., 1986; Dahl *et al*., 1991). *In vivo* data on primates and *in vitro* data on human tissues suggest that humans and other primates are closer to rats than mice with regard to the metabolism of butadiene and resultant body burden of 1,2-epoxy-3-butene (Sabourin *et al*., 1992).

There have been no reports of skin or eye irritation for butadiene, and it has a low acute and subchronic toxicity. The target organs in mice are the central nervous system and bone marrow. A NOAEL of 625 ppm 1406 mg/m^3) was established following exposure for 6 hrs/day, 5 days/week for 14 weeks (NTP, 1984). Exposure of rats and guinea pigs to butadiene at 0, 600, 2300 or 6700 ppm (0, 1350, 5175, 15075 mg/m^3), 7.5 hrs/day, 6 days/week for 8 months, resulted in reduced body-weight gain at the top concentration (Carpenter *et al*., 1944). No effects were reported in animals exposed to 600 or 2300 ppm (1350 or 5175 mg/m^3) butadiene.

Fertility studies revealed no adverse effects in guinea pigs, rabbits and rats at exposure concentrations up to 6700 ppm (15075 mg/m^3) for 8 months (Carpenter *et* al., 1944). Developmental toxicity studies have shown no effects at exposures below those causing maternal toxicity (Hackett *et* al., 1987a,b; Irvine, 1981,1982).

Butadiene has been tested in a wide variety of *in vitro* and *in vivo* genotoxicity assays. It is not genotoxic in the absence of metabolic activation but its epoxide metabolites react with DNA to form alkylation products and interstrand cross-links (Arce *et al*., 1990). *In vivo* assays have generally produced positive results in mice and negative results in rats (Cunningham *et al*., 1986; Jelitto *et al*., 1989; Tice *et al*., 1987).

The carcinogenicity of butadiene has been studied in Sprague-Dawley rats (Owen, 1981a, b; Owen *et al*., 1987) and in B6C3F1 mice (NTP, 1984; Melnick and Huff, 1992). Butadiene is a potent carcinogen in mice, with tumours found in lungs of females exposed at 6.25 ppm (14.1 mg/m^3), 6 hrs/day, 5 days/week for up to 2 years (Melnick and Huff, 1992). This was the lowest concentration tested. At higher concentrations, butadiene produced a dose-related incidence of multiple types of tumours in both sexes, including T-cell lymphoma, haemangiosarcoma, alveolar bronchiolar neoplasms, squamous cell neoplasm, hepatocellular neoplasm and Harderian gland neoplasm. In contrast, in rats exposed to butadiene at 1000 ppm (2250 mg/m^3) for up to 2 years, a statistically significant increase in tumour incidence was only seen in the mammary gland, the majority of the tumours being benign (Owen and Glaister, 1990). At 8000 ppm (18000 mg/m^3), tumours were also seen in the pancreas, thyroid and Leydig cells of the testes.

In several studies in mice and rats, reviewed by Himmelstein *et al.* (1997) and Pacchierotti *et al*. (1998) a correlation between the levels of the butadiene monoepoxide adduct N-(2-hydroxy-3-butenyl)valine in haemoglobin and the butadiene concentration has been observed (e.g. Osterman-Golkar *et al*. 1993). The dose-response curve for rats became flatter above 500 ppm (1125 mg/m^3).

This haemoglobin adduct has also been detected in workers (Osterman-Golkar *et al.* 1993, 1996, Sorsa *et al.* 1996). Levels were 0.05, 0.16, 0.5 and $\leq$ 2.6 pmol/g for butadiene exposures of less than 0.5, 5, $\leq$3 and $\leq$3.5 ppm (1.125, 11.25, $\leq$6.75 and $\leq$7.875 mg/m^3) respectively. The levels for control persons were below the detection limit of 0.5 pmol/g haemoglobin.

In two workers exposed to butadiene below 3 ppm (6.75 mg/m^3), the adduct level of the diepoxide was five times that of the control value and about 70 times that of the monoepoxide adduct (Perez *et al*., 1997). In rats, the ratio of the diepoxide and monoepoxide adducts ranged from 4 to 26, and the level of the diepoxide adducts was the same after 50 ppm and 500 ppm (112.5 and 1125 mg/m^3) exposure (Perez *et al*., 1997), which indicates saturation of metabolic formation of the reactant.

Studies of HPRT mutations and chromosomal aberrations in the lymphocytes of persons exposed to butadiene were reviewed by Himmelstein *et al*. (1997) and Pacchierotti *et al*. (1998). These yielded contradictory results which may be explained by differences in exposure levels and detection methods.

A number of cancer epidemiology studies on occupational cohorts with exposure to 1,3-butadiene have been conducted. A mortality study of almost 3.000 U.S. workers employed for at least six months, between 1942 and 1994, in the manufacture of 1,3-

butadiene was recently updated. All-cancer mortality was not increased (282 deaths, SMR=0.92, 95%CI=0.82-1.04). Lymphohaematopoietic cancers were in excess (42 deaths, SMR=1.47, 95%CI=1.06-1.98); 31 of these deaths were in workers employed in operating units, laboratories and maintenance with a potential for highest exposure (SMR=1.72, 95%CI=1.17-2.44). The SMRs for the lymphohaematopoietic cancers had an inverse relation (decreased) with length of employment and duration of employment. No significant increases at any other cancer site were seen (Divine and Hartman 1996). A smaller cohort of 364 men assigned to 1,3-butadiene production was also studied in the USA. All-cancer mortality was not increased (48 deaths, SMR=1.05, 95%CI=0.78-1.40); lymphatic and haematopoietic cancers showed a non-significant increase (7 deaths, SMR=1.75, 95%CI= 0.70-3.61), whereas mortality from lymphosarcoma and reticulosarcoma was high among workers with duration of employment > 2 years, even in comparison with local rates (4 deaths, SMR=5.77, 95%CI=1.57-14.8). The largest occupational cohort study, recently updated, included some 16.000 men employed for at least one year in eight styrene-butadiene rubber plants in the USA and Canada (Delzell et al 1996, Sathiakumor et al 1998). Cancer mortality was lower than expected (950 deaths, SMR=0.93, 95%CI=0.87-0.99). There were 11 lymphosarcoma (SMR=0.80, 95%CI=0.40-1.44) and 42 other lymphatic cancers (SMR=0.97, 95%CI=0.70-1.52). Leukaemia deaths were in excess among “ever hourly subjects” (45 deaths, SMR=1.43, 95%CI=1.04-1.91), and most clearly after 10 years worked and 20 years since hire (28 deaths, SMR=2.24, 95%CI=1.49-3.23). An analysis of leukaemia mortality by cumulative exposure estimates to styrene, butadiene and benzene was performed in a largely overlapping cohort of workers (Macaluso et al 1996). A statistically significant trend for leukaemia deaths by cumulative exposure to butadiene, adjusted by age, gender, styrene exposure and race was found (RRs of 1.0, 2.0, 2.1, 2.4, 4.5 for exposure to 0, 0-1, 1-19, 2080, 80+ ppm-years). No dose-related increases were seen for styrene and benzene cumulative exposure.

Subsequently, the procedures for exposure estimation to 1,3-butadiene (BD) and styrene (STY) in this cohort were revised, and exposure estimates for sodium dimethyldithio-carbamate (DMDTC), used as a shortstop in synthetic rubber polymerisation, and considered by some a possibly relevant confounding factor, were also developed (Delzell *et al.* 2001). Leukaemia mortality was positively associated with BD ppm-years (RRs of 1.0, 1.2, 2.0 and 3.8 for exposure to 0, 0-86.3, 86.3-362.2, and 362.2+ ppm) after controlling for other agents. A positive association was also seen for STY, but the relation disappeared after controlling for the other two agents. DMDTC was positively associated with leukaemia, even after adjusting for BD and STY, however, no monotonic D-R relation was found (RRs of 1.0, 2.3, 4.9, and 2.9 for 0, 0-566.6, 566.6-1395.1 and 1395.1+ mg/m^3). The independent effect of each agent was difficult to evaluate.

In 1998 a working group convened by the International Agency for Research on Cancer reviewed and evaluated all the available scientific information and concluded that the evidence regarding carcinogenicity of 1,3-butadiene was sufficient in animal experiments and limited in human epidemiological studies (IARC, 1998). Other data suggested that the metabolism was qualitatively similar in human beings and experimental animals; in mammals, epoxy metabolites of 1,3-butadiene interact with DNA. The overall evaluation was that 1,3-butadiene is probably carcinogenic to humans (category 2A).

On the basis of the IARC evaluation and the subsequently published cancer epidemiology studies, SCOEL agreed to consider 1,3-butadiene as probably carcinogenic to humans and hence adopted the established approach for carcinogenic substances (see SCOEL key documents). In line with this approach, the risk entailed in working for a lifetime at various average airborne concentrations of 1,3-butadiene was estimated based on data from the recent epidemiological studies in styrene-butadiene rubber industry workers, which included quantitative estimates of exposure to 1,3-butadiene (Delzell et al. 1996 and 2001, Macaluso et al. 1996, ECETOC 1997).

A paper by Zocchetti (2002) presented a set of estimates of leukaemia risk in terms of SMR's and excess deaths based on all available dose-response models published in the open literature at that time. There actually is more recent exposure information published by Macaluso et al. 2004, however no risk estimates have been associated with the newly estimated exposure categories and no risk assessment can be based on those incomplete data. Two different methods were used to estimate a risk coefficient (β) per unit of exposure. One was based on excess relative risk "linear model" without a threshold. To obtain the risk coefficient *per* unit of exposure, each observed excess risk (RR or SMR-1) was divided by the associated cumulative exposure. When a set of median cumulative exposures and associated relative risks were available, the risk coefficient *per* unit exposure was obtained by applying a linear interpolation to the data *via* Poisson regression techniques. The second method was a "step model" in which the risk coefficient per exposure unit remains constant in a certain range of exposure and then changes abruptly (step) moving to the next range. Here, ranges of cumulative exposure above 0.0 ppm and associated relative risk estimates were combined with a dummy variable indicating a specific range.

The number of *expected* deaths from leukaemia in the absence of the exposure of interest was estimated in a reference male population (England and Wales) with a life-table approach, taking into account the mortality decline that naturally occurs in an ageing population. Assuming that exposure lasts for a working life (40 years, between the ages of 20 and 65), the number of *predicted* leukaemia deaths associated with different cumulative exposure to 1,3-butadiene were calculated, using the estimated coefficients indicating the excess relative risk for each ppm of cumulative exposure, for a population of 1.000 exposed male workers between the ages of 20 and 85. Predicted and expected deaths were compared, and results expressed as either additional deaths (predicted deaths - expected deaths) or excess SMR (predicted deaths/expected deaths). The "step model" was considered the most appropriate (Zocchetti 2002).

The annexed table summarises the results of the risk estimates for leukaemia using the step model, based on the exposure-response relation models published by Delzell et al. 2001. In the first column, the table from which the basic epidemiological data were taken is reported. In the second column, the RR or SMR and the excess (RR or SMR-1) risk are indicated. In the third column, the exposure associated in the literature with the reported risk is shown. Then comes the assessment of the number of excess deaths and excess SMR associated with lifetime exposure to 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10 ppm of BD, obtained with the different models. Asterisks specify exposure estimates that were based on intensities experienced only either below or above 100ppm.

The minimum and maximum excess leukaemia deaths estimates for different exposure levels are summarized in a final table in the ANNEX.

RECOMMENDATION:

1,3-butadiene was tested adequately for carcinogenicity in mice and rats by inhalation. In independent experiments in mice, tumours were induced in both sexes, at multiple sites, at concentrations ranging from 6.25 to 1,250 ppm. Exposure-related increases were observed for numerous cancer types, including heart angiosarcoma, malignant lymphomas, lung alveolar/bronchiolar adenomas and carcinomas, and forestomach papillomas and carcinomas. In one experiment in rats, multiple-site increased tumour incidence was only seen at 8000ppm.

The recent updating of the follow-up on a large North-American cohort of styrene-butadiene rubber workers revealed a greater than twofold increase in leukaemia mortality among long-term workers, with a significant dose-response relationship to cumulative exposure to butadiene after adjusting for styrene and dimethyldithio-carbamate exposure; the independent effect of each agent could not be firmly evaluated. Two smaller cohort studies of butadiene production workers showed slight excesses of lymphohaemopoietic cancers, but these were not considered to be associated with butadiene exposure.

On the basis of the available evidence, the SCOEL agreed that 1,3-butadiene should be treated as a possible human carcinogen, operating via a genotoxic mechanism. Hence, according to the established approach for such carcinogenic substances, the excess risk entailed in exposure during a working life to various concentrations of butadiene has been calculated using various models; the results are illustrated in the annexed table.

As an example of how to read the annexed table, the calculated additional leukaemia risk associated with exposure to – say - 1ppm 1,3-butadiene for a 40-year working life, according to the "step model", and using the exposure estimates and their associated RRs reported in the most recent epidemiological study (Delzell et al. 2001), may be illustrated as follows: "In a population of 1.000 adult males experiencing a mortality rate similar to that of the male population of England and Wales, occupational exposure to 1 ppm of 1,3-butadiene for a working life (40 years between the ages of 25 and 65), will cause from 0.0 to 10.78 extra leukaemia deaths between the ages 25-85 years, in addition to the 5 leukaemia deaths expected to occur in the absence of exposure to 1,3-butadiene."

No STEL or "skin" notation was considered necessary.

At the levels discussed, no measurement difficulties are anticipated.

KEY BIBLIOGRAPHY:

Acquavella, J. F. (1989). The paradox of butadiene epidemiology. Exp Pathol. 37, 114-118.

Acquavella, J. F. (1992). Butadiene epidemiology program. Presentation to US EPA/CMA meeting. April 8, 1992. Monsanto, St Louis. Missourri.

Arce, G. T., Vincent, D. R., Cunningham, M. J., Choy, W. N. and Sariff, A. M. (1990). In vitro and in vivo genotoxicity of 1,3-butadiene and metabolites. Environ. Health Perspect. 86, 75-78.

Bond, J. A., Dahl, A. R., Henderson, R. F., Dutcher, J. S., Mauderly, J. L. and Birnbaum, L. S. (1986). Species differences in the disposition of inhaled butadiene. Toxicol. Appl. Pharmacol. 84, 617-627.

Carpenter, C. P., Shaffer, C. B., Weil, C. S. and Smyth Jr., H. F. (1944). Studies on the inhalation of 1,3-butadiene: with a comparison of its narcotic effect with benzol, toluol and styrene and a note on the elimination of styrene by the human. J. Industr. Hyg. 26, 69-78.

Cole, P., Delzell, E. and Acquavella, J. F. (1992). Exposure to butadiene and lymphatic and hematopoietic cancer. Epidemiology 4, 96-103.

Csanády, G. A., Guengerich, F. P and Bond, J. A. (1992). Comparison of the biotransformation of 1,3-butadiene and its metabolite, butadiene monoepoxide, by hepatic and pulmonary tissues form humans, rats and mice. Carcinogenesis 13, 1143-1153.

Cunningham, M. J., Choy, W. N., Arce, G. T., Richard, L. B., Vlachos, D. A., Kinney, L. A. and Sarrif, A. M. (1986). In vivo sister chromatid exchange and microneucleus induction with 1,3-butadiene in B6C3F2 mice and Sprague Dawley rats. Mutagenesis 1, 449-452.

Dahl, A. R., Sun, J. D., Bender, M. A., Nirbaum, L. S., Bond, J. A., Griffith, W. C., Mauderly, J. L., Muggenburg, B. A., Sabourin, P. J. and Henderson, R. F. (1991). Toxicokinetics of inhaled 1,3-butadiene in monkeys: comparison to toxicokinetics in rats and mice. Toxicol. Appl. Pharmacol. 110, 9-19.

Dankovic, D. A., Smith, R. J., Seltzer, J., Bailer, A. J. and Stayner, L. T. (1993). A quantitative assessment of the risk of cancer associated with exposure to 1,3-butadiene, based on a low dose inhalation study in B6C3F1 mice. IARC Scientific Publ. 127, 335-344.

DECOS (Dutch Expert Committee for Occupational Standards) (1990). Health-based recommended occupational exposure limits for 1,3-butadiene. DG Labour, Min. Social Affairs and Employment, Voorburg.

Delzell, E., Sathiakumar, N., Hovinga, M., Macaluso, M., Julian, J., Larson, R., Cole, P., Muir, D.C.F. (1996). A follow-up study of synthetic rubber workers. Toxicology 113, 182-189.

Delzell, E., Macaluso, M., Sathiakumar, N., Matthews R., (2001). Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. Chemico-biological Interactions 135/6, 515-534.

Divine, B. J. and Hartman, C. M. (1996). Mortality update of butadiene production workers. Toxicology 113, 169-181.

ECETOC (1992). 1,3-Butadiene Criteria Document. Special Report No. 4, European Centre for Exotoxicology and Toxicology of Chemicals, Brussels.

ECETOC (1997). Occupational Exposure Limits. Criteria Document for 1,3-Butadiene. EUR 17772 EN.

Environ (1986). Assessment of the potential risks to workers from exposure to 1,3-butadiene. Chemical Manufacturers Association. Washington DC.

EPA (US Environmental Protection Agency) (1985a). Assessment of cancer risks to workers exposed to 1,3-butadiene monomer and production of synthetic rubbers, plastics and resins. US EPA, Risk Management Branch, Existing Chemical Assessment Division, OTS, Washington, DC.

EPA (US Environmental Protection Agency) (1985b). Mutagenicity and carcinogenicity assessment of 1,3-butadiene, final report EPA 600/8-85-0045. US EPA, Office of Health and Environmental Assessment. Washington, DC.

Hackett, P. L., Sikov, M. R., Mast, T. J., Brown, M. G., Buschbom, R. L., Clark, M. L., Decker, J. K., Evanoff, J. J., Rommereim, R. L., Rowe, S. E. and Westerberg, R. B. (1987a). Inhalation development toxicology studies of 1,3-butadiene in the rat, final report NIH-401-ES-40131, prepared by Batelle, Pacific Northwest Lab. NIEHS, NTP, Research Triangle Park NC.

Hackett, P. L., Sikov, M. R., Mast, T. J., Brown, M. G., Buschbom, R. L., Clark, M. L., Decker, J. K., Evanoff, J. J., Rommereim, R. L., Rowe, S. E. and Westerberg, R. B. (1987b). Inhalation development toxicology studies of 1,3-butadiene in mice, final report NIH-401-ES-40131, prepared by Batelle, Pacific Northwest Lab. NIEHS, NTP, Research Triangle Park NC.

Himmelstein MW, Acquavellea JF, Recio K, Medinsky M, Bond JA (1997) Toxicology and epidemiology of 1,3-butadiene. Crit Rev Toxicol 27: 1–108

IARC (International Agency for Research on Cancer) (1992). 1,3-Butadiene. In: IARC Monographs on the evaluation of carcinogenic risks to humans. 54. Occupational exposure to mists and vapours from strong inorganic acids and other industrial chemicals. IARC, Lyon, pp237-285.

IARC (International Agency for Research on Cancer) (1998). Re-evaluation of some industrial chemicals. Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 71, in preparation.

ICF/Clement (1986). Characterisation of risks associated with occupational exposure to 1,3-butadiene, final report. OSHA, US Dept. Lanor, Washington DC.

Irvine, L. F. H. (1981). 1,3-Butadiene: inhalation teratogenicity study in the rat, final report 2788-522/3. Hazleton Lab Europe. The International Institute of Synthetic Rubber Producers, Houston TX.

Irvine, L. F. H. (1982). 1,3-Butadiene: inhalation teratogenicity study in the rat, addendum to final report 2788-522/3. Hazleton Lab Europe. The International Institute of Synthetic Rubber Producers, Houston TX.

Jelitto, B., Vangala, R. R., Laib, R. J. (1989). Species difference in DNA damage by butadiene: role of diepoxybutane. Arch. Toxicol;. Suppl. 13, 246-249.

Kreiling, R., Laib, R. J., Filser, J. G., and Bolt, H. M. (1986). Species differences in butadiene metabolism between mice and rats evaluated by inhalation pharmacokinetics. Arch. Toxicol. 58, 235-238.

Kreiling, R., Laib, R. J., Filser, J. G., and Bolt, H. M. (1987). Inhalation pharmacokinetics of 1,2-epoxybutene-3 reveal species differences between rats and mice sensitive to butadiene-induced carcinogenesis. Arch. Toxicol. 61, 7-11.

Kreuzer, P. E., Kessler, W., Welterm H. F., Baur, C. and Filser, J. F., (1991). Enzyme specific kinetics of 1,2-epoxybutene-3 in microsomes and cytosol form livers of mouse, rat and man. Arch. Toxicol. 65, 59-67.

Landrigan, P. J. (1990). Critical assessment of epidemiological studies on the human carcinogenicity of 1,3-butadiene. Environ. Health Perspect. 86, 143-148.

Macaluso, M., Larson, R., Delzell, E., Sathiakumar, N., Hovinga, M., Julian, J., Muir, D., Cole, P. (1996). Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. Toxicology 113, 190-202.

M. Macaluso et al. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber worker. *Journal of Occupational and Environmental Hygiene*, 1: 371–390. 2004)

Malvoisin, E., Lhoest, G., Poncelet, F., Roberfroid, M. and Mercier, M. (1979). Identification and quantification of 1,2-epoxybutene-3 as the primary metabolite of 1,3-butadiene. J. Chromatog. 178, 419-425.

Malvoisin, E. and Roberfroid, M. (1982). Hepatic microsomal metabolism of 1,3-butadiene. Xenobiotica. 12, 137-144.

Matanoski, G. M., Santos-Burgoa, C. and Schwartz, L. (1990). Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). Environ. Health Perspect. 86, 107-117.

Melnick, R. C. and Huff, J. (1992). 1,3-Butadiene: toxicity and carcinogenicity in laboratory animals and in humans. Rev. Environ, Contam. Toxicol. 124, 111-142.

NTP (US National Toxicology Program) (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). TR 288. NIH 84-2544, NTP, Research Triangle Park NC.

Osterman-Golkar SM, Bond JA, Ward JB, Legator MS (1993) Use of hemoglobin adducts for biomonitoring exposure to 1,3-butadiene. in: Sorsa M, Peltonen K, Vainio H, Hemminki K (Eds) Butadiene and styrene: assessment of health hazards, IARC Scientific Publications No 127, IARC, Lyon, 127–134

Osterman-Golkar S, Peltonen K, Anttinen-Klemetti T, Hindsø Landin H, Zorcec V, Sorsa M (1996) Haemoglobin adducts as biomarkers of occupational exposure to 1,3-butadiene. Mutagenesis 11: 145–149

Owen, P. E. (1981a). The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months. Hazleton Laboratories Europe, rep 2653-522/2. International Institute of Synthetic Rubber Producers, Houston TX.

Owen, P. E. (1981b). The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months. Hazleton Laboratories Europe, rep 2653-522/3. International Institute of Synthetic Rubber Producers, Houston TX.

Owen, P. E. (1987). Inhalation toxicity studies with 1,3-butadiene: 3. two year toxicity/carcinogenicity study in rats. Am. Ind. Hyg. Assoc. J. 48, 407-413.

Owen, P. E. and Glaister, J. R. (1990). Inhalation toxicity and carcinogenicity of 1,3-butadiene in Sprague-Dawley rats. Environ. Health Perspect. 86, 19-25.

Pacchierotti F, Adler I-D, Anderson D, Brinkworth M, Demopoulos, Lähdetie J, Osterman-Golkar S, Peltonen K, Russo A, Tates A, Waters R (1998) Genetic effects of 1,3-butadiene and associated risk for heritable damage. Mutat Res 397: 93–115

Pemble, S., Schroeder, K. R.,Spencer, S. R., Meyer, D. J., Hallier, E., Bolt, H. M., Ketterer, B. and Taylor, J. B. (1994). Human glutathione S-transferase theta (GSTT1): CDNA cloning and the characterisation of a genetic polymorphism. Biochem. J. 300, 271-276.

Pérez HL, Lädehtie J, Landin HH, Kilpeläinen I, Koivisto P, Peltonen K, Osterman-Golkar S (1997) Haemoglobin adducts of epoxybutanediol from exposure to 1,3-butadiene or butadiene epoxides. Chem Biol Interact 105: 181–198

Sabourin, P. L., Burka, L. T., Bechtold, W. E., Dahl, A. R., Hoover, M. D., Chang, I, Y. and Henderson, R. F. (1992). Species differences in urinary butadiene metabolites: identification of 1,2-dihydroxy-4-(N-acetylcysteinyl)-butane, a novel metabolite of butadiene. Carcinogenesis 13, 1633-1638.

Santos-Burgoa, C., Matanoski, G. M., Zeger, S. and Swartz, L. (1992). Lympho-hematopoitic cancer in styrene-butadiene polymerization workers. Am. J. Epidemiol. 136, 843-854.

Sathiakumar, N., Delzell, E., Hovinga, M., Macaluso, M., Julian, J. A., Larson, R., Cole, P. and Muir, D. C. (1998). Mortality from cancer and other causes of death among synthetic rubber workers. Occup Environ Med.55, 230-235.

Shell Oil (1990). Comments on an alternative risk assessment for OSHA-proposed butadiene standard, response to OSHA's notice of proposed rulemaking on occupational exposure to 1,3-butadiene in August 1990. US Fed. Reg. 55, 32735-32826.

Sorsa M, Osterman-Golkar S, Peltonen K, Saarikoski ST, Šrám R (1996) Assessment of exposure to butadiene in the process industry. Toxicology 113: 77–83

Thier, R., Persmark, S. E., Taylor, J. B., Ketteret, B. and Guengerich, F. P. (1994). Mutagenicity of 1,2,3,4-butadiene diepoxide is altered by mammalian theta-class glutathione S-transferase. Naunym-Schmeiderberg's Arch. Pharmacol., Suppl. 349, R121, abstract 482.

Tice, R. R., Boucher, R., Luke, C. A., Selby, M. D., (1987). Comparative cytogenetic analysis of bone marrow damage induced in male B6C3F1 mice by multiple exposures to gaseous 1,3-butadiene. Environ. Mutagen. 9, 235-250.

Turnbull, D., Rodricks, J. V. and Brett, S. M. (1990). Assessment of the potential risk to workers from exposure to 1,3-butadiene. Environ. Health Perspect. 86, 159-171.

Zocchetti, C. (2002). Risk assessment for 1,3-butadiene. SCOEL internal document SEG/INF/258

Data taken from published literature						Number of EXCESS DEATHS and SMR based on risk assessment													
						TWA (ppm)													
						0,1		0,2		0,5		1		2		5		10	
STUDY			EXCESS	CUM.EXP.		EXCESS		EXCESS		EXCESS		EXCESS		EXCESS		EXCESS		EXCESS	
CAUSE OF DEATH		RR/SMR	RR/SMR	Median	Range	DEATHS	SMR	DEATHS	SMR	DEATHS	SMR	DEATHS	SMR	DEATHS	SMR	DEATHS	SMR	DEATHS	SMR
Leukaemia	Table 2	1,2	0,2		0-86,3														
	mod 1	2,0	1,0		86,3-362,2														
		3,8	2,8		362,2+														
	Step model					1,02	1,20	1,02	1,20	1,02	1,20	1,02	1,20	1,02	1,20	4,82	1,95	7,38	2,45
Leukaemia	Table 2	1,3	0,3		0-86,3														
	mod 2	1,3	0,3		86,3-362,2														
		2,3	1,3		362,2+														
	Step model					1,53	1,30	1,53	1,30	1,53	1,30	1,53	1,30	1,53	1,30	1,53	1,30	2,88	1,56
Leukaemia	Table 3	1,1	0,1		0-37,8														
* <100	mod 3	2,8	1,8		37,8-96,3														
		3,0	2,0		96.3+														
	Step model					0,51	1,10	0,51	1,10	0,51	1,10	2,39	1,47	8,54	2,68	9,84	2,94	10,01	2,97
Leukaemia	Table 3	2,1	1,1		0-46,5														
** >100	mod 4	2,8	1,8		46,5-234,3														
		5,8	4,8		234,3+														
	Step model					5,61	2,10	5,61	2,10	5,61	2,10	5,61	2,10	8,52	2,68	9,02	2,77	21,45	5,26
Leukaemia	Table 4	2,5	1,5		0-46,5														
** >100	mod 5	2,9	1,9		46,5-234,3														
		5,2	4,2		234,3+														
	Step model					7,64	2,50	7,64	2,50	7,64	2,50	7,64	2,50	9,30	2,83	9,58	2,88	19,11	4,79
Leukaemia	Table 4	1,6	0,6		0-46,5														
** >100	mod 6	1,7	0,7		46,5-234,3														
		3,6	2,6		234,3+														
	Step model					3,06	1,60	3,06	1,60	3,06	1,60	3,06	1,60	3,48	1,68	3,55	1,70	11,48	3,26
Leukaemia	Table 4	2,3	1,3		0-46,5														
** >100	mod 7	2,2	1,2		46,5-234,3														
		4,3	3,3		234,3+														
	Step model					6,62	2,30	6,62	2,30	6,62	2,30	6,62	2,30	6,21	2,22	6,13	2,20	14,83	3,93
Leukaemia	Table 4	1,0	0,0		0-37,8														
* <100	mod 8	2,2	1,2		37,8-96,3														
		2,0	1,0		96,3+														
	Step model					0,00	1,00	0,00	1,00	0,00	1,00	1,33	1,26	5,68	2,11	5,00	1,98	5,06	1,99
Leukaemia	Table 4	0,8	-0,2		0-37,8														
* <100	mod 9	1,8	0,8		37,8-96,3														
		1,9	0,9		96,3+														
	Step model					-1,02	0,80	-1,02	0,80	-1,02	0,80	0,08	1,02	3,72	1,73	4,41	1,86	4,51	1,88

Leukaemia	Table 4	1,0	0,0	0-37,8															
* <100	mod 10	2,2	1,2	37,8-96,3															
		2,2	1,2	96,3+															
	Step model				0,00	1,00	0,00	1,00	0,00	1,00	1,33	1,26	5,68	2,11	5,94	2,17	6,03	2,18
Leukaemia	Table 5	1,2	0,2	0-86,3															
	mod 11	1,5	0,5	86,3-362,2															
		2,4	1,4	362,2+															
	Step model				1,02	1,20	1,02	1,20	1,02	1,20	1,02	1,20	1,02	1,20	2,45	1,48	3,71	1,73
Leukaemia	Table 5	1	0	0-86,3															
	mod 12	1,2	0,2	86,3-362,2															
		2,2	1,2	362,2+															
	Step model				0,00	1,00	0,00	1,00	0,00	1,00	0,00	1,00	0,00	1,00	0,95	1,19	2,34	1,46
Leukaemia	Table 6	1,1	0,1	0-38,7															
	mod 13	1,4	0,4	38,7-123,6															
		2,0	1,0	123,6-287,3															
		2,9	1,9	287,3-641,9															
		4,7	3,7	641,9+															
	Step model				0,51	1,10	0,51	1,10	0,51	1,10	0,77	1,15	1,93	1,38	4,40	1,86	7,75	2,52
Leukaemia	Table 6	1,1	0,1	0-38,7															
	mod 14	1,0	0,0	38,7-123,6															
		1,3	0,3	123,6-287,3															
		2,0	1,0	287,3-641,9															
		3,7	2,7	641,9+															
	Step model				0,51	1,10	0,51	1,10	0,51	1,10	0,43	1,08	0,04	1,01	1,22	1,24	3,67	1,72
Leukaemia	Table 6	1	0	0-38,7															
	mod 15	0,9	-0,1	38,7-123,6															
		1,1	0,1	123,6-287,3															
		1,5	0,5	287,3-641,9															
		2,6	1,6	641,9+															
	Step model				0,00	1,00	0,00	1,00	0,00	1,00	-0,09	0,98	-0,47	0,91	0,31	1,06	1,73	1,34
Leukaemia	Table 6	1,3	0,3	0-38,7															
	mod 16	0,9	-0,1	38,7-123,6															
		1,0	0,0	123,6-287,3															
		1,7	0,7	287,3-641,9															
		3,4	2,4	641,9+															
	Step model				1,53	1,30	1,53	1,30	1,53	1,30	1,19	1,23	-0,36	0,93	-0,05	0,99	2,21	1,43
Leukaemia	Table 7	1,6	0,6	0-30,6															
** >100	mod 17	3,8	2,8	30,6-56,6															
		2,4	1,4	56,6-173,3															
		4,9	3,9	173,3-356,9															
		5,6	4,6	356,9+															
	Step model				3,06	1,60	3,06	1,60	3,06	1,60	8,99	2,77	9,14	2,80	11,67	3,30	19,92	4,95
Leukaemia	Table 7	1,9	0,9	0-30,6															
** >100	mod 18	4,2	3,2	30,6-56,6															
		2,4	1,4	56,6-173,3															
		4,7	3,7	173,3-356,9															
		5,8	4,8	356,9+															

	Step model				4,59	1,90	4,59	1,90	4,59	1,90	10,78	3,12	9,88	2,94	11,40	3,25	19,65	4,89
Leukaemia	Table 7	1,2	0,2	0-30,6														
** >100	mod 19	2,4	1,4	30,6-56,6														
		1,4	0,4	56,6-173,3														
		2,8	1,8	173,3-356,9														
		3,5	2,5	356,9+														
	Step model				1,02	1,20	1,02	1,20	1,02	1,20	4,27	1,84	3,61	1,71	4,66	1,91	9,80	2,93
Leukaemia	Table 7	1,7	0,7	0-30,6														
** >100	mod 20	3,2	2,2	30,6-56,6														
		1,7	0,7	56,6-173,3														
		3,4	2,4	173,3-356,9														
		4,8	3,8	356,9+														
	Step model				3,57	1,70	3,57	1,70	3,57	1,70	7,62	2,50	6,01	2,18	6,81	2,34	13,85	3,73
Leukaemia	Table 8	1	0	0-38,7														
	mod 21	1,5	0,5	38,7-287,3														
		3,4	2,4	287,3+														
	Step model				0,00	1,00	0,00	1,00	0,00	1,00	0,43	1,08	2,36	1,46	2,48	1,49	8,48	2,67
Leukaemia	Table 8	1	0	0-38,7														
	mod 22	1,0	0,0	38,7-287,3														
		2,0	1,0	287,3+														
	Step model				0,00	1,00	0,00	1,00	0,00	1,00	0,00	1,00	0,00	1,00	0,00	1,00	3,15	1,62
Leukaemia	Table 9	1	0	0-38,7														
	mod 23	1,1	0,1	38,7-287,3														
		2,6	1,6	287,3+														
	Step model				0,00	1,00	0,00	1,00	0,00	1,00	0,09	1,02	0,47	1,09	0,50	1,10	5,23	2,03

	Number of EXCESS DEATHS and SMR based on risk assessment													
	TWA (ppm)													
	0,1		0,2		0,5		1		2		5		10	
	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR
Min.	**-1,02**	**0,80**	**-1,02**	**0,80**	**-1,02**	**0,80**	**-0,09**	**0,98**	**-0,47**	**0,91**	**-0,05**	**0,99**	**1,73**	**1,34**
Max.	**7,64**	**2,50**	**7,64**	**2,50**	**7,64**	**2,50**	**10,78**	**3,12**	**9,88**	**2,94**	**11,67**	**3,30**	**21,45**	**5,26**

*** <100: Exposure cumulated at intensities below 100ppm only**
**** >100: Exposure cumulated at intensities above 100ppm only**