Recommendation from the Scientific Committee

on Occupational Exposure Limits

for 2-Butanone

8 hour TWA:	200 ppm (600 mg/m^3)
STEL (15 mins):	300 ppm
Additional classification:	"skin"

Substance identification:

Butanone **$CH_3CH_2CHOCH_3$**

Synonyms : Methylethylketone, MEK, 2-butanone, methyl acetone

EINECS N° : 201-159-0

EEC N° : 606-002-00-3 Classification: F; R11 Xi: R36/37

CAS N° : 78-93-3

MWt : 72.12

Conversion factor (20°C, 101kPa): 3.00 mg/m^3 = 1 ppm

Occurrence/use:

Butanone (MEK) is, at ambient temperature, a colourless, volatile, water-miscible, highly flammable liquid with a characteristic odour resembling that of acetone. It has a MPt of -87°C, a BPt of 79.6°C and a vapour pressure of 10.3kPa at 20°C which leads to a saturation concentration of 10% (100,000 ppm) in air at 20°C under normal conditions. The flash point is below 0°C. The explosive limits are 1.8% and 12% by volume in air. The odour threshold varies between 2 and 83 ppm (6 and 250 mg/m^3).

MEK occurs naturally in very low amounts, possibly as a result of fatty acid metabolism. MEK is a high volume industrial solvent with a production rate in the European Union greater than 1000 tonnes per annum. MEK is mainly used as a solvent constituent of coatings, but also in extraction processes, in azeotropic separations and as

an intermediate for the preparation of catalysts, flavours, antioxidants, perfumes and in the manufacture of ethyl-n-amylketone and MEK-peroxide. It is a solvent of abuse (sniffers).

Health Significance:

The SCOEL reviewed the document of the Dutch Expert Committee for Occupational Standards. Taken together with a detailed analysis of the available human studies in workers and in volunteers, the SCOEL regarded the available data as sufficient to evaluate MEK.

MEK is rapidly absorbed through human skin. Quantitative data are not available, but it has been reported that MEK was detected in expired air 3 min after start of dermal exposure (Munies and Wurster, 1965; Wurster and Munies, 1965).

MEK shows a low oral (LD50: 2400 to 5600 mg/kg) and dermal (LD50: 13000 mg/kg) acute toxicity in animals. Rat LCLo values have been determined as 4000 ppm (12000 mg/m^3) with a 2 hour exposure and 2000 ppm (6000 mg/m^3) with a 4 hour exposure.

In an interlaboratory test with topical application on rats, MEK was rated to be an eye irritant and not a skin irritant (Weil and Scala, 1971). No skin sensitising properties of MEK could be shown in the mouse ear swelling test (Gad *et al*., 1986). Dose-related behavioural changes have been shown in mice. IC50 values (50% decrease in response times) have been estimated to be approximately 2000 ppm (6000 mg/m^3) and 2900 ppm (8700 mg/m^3) in separate studies (De Ceaurriz *et al*, 1983; Glowa and Dews, 1987).

Subchronic studies with a limited number of rats (12) continuously exposed for 24h/day to 1133 ppm (3400 mg/m^3) for between 55 days and 5 months showed no peripheral neurotoxicity. From these limited studies a NOAEL of 1133 ppm (3400 mg/m^3) could be concluded (Saida *et al*., 1976).

The subchronic inhalation study of Cavender *et al*. (1983) on groups of 15 male and 15 female F344 rats, exposed to MEK at 0, 1250, 2500, 5000 ppm (0, 3750, 7500 and 15000 mg/m^3), 6h/day, 5 days/week for 90 days is regarded as the key animal study. There was a depression of mean body weight and a slight but significant increase in relative and absolute liver weight in the high dose group. The NOAEL was 2500 ppm (7500 mg/m^3). At all applied concentrations no signs of upper respiratory irritation or neuropathological/pathological lesions could be detected.

Mutagenicity tests have been negative (Zeiger *et al*., 1992) with the single exception of the induction of aneuploidy in yeast at relative high concentration (3.5% in the culture medium) (Zimmerman *et al*., 1985).

No study on carcinogenicity is available. The reproductive toxicity cannot be evaluated finally, but no significant embryotoxicity or teratogenic effect could be demonstrated in one study (rats) with exposures of from 400 to 3000 ppm (1200 to 9000 mg/m^3) MEK for 7h/day during the period of major organogenesis (Deacon *et al*., 1981).

Animal data show that MEK potentiates the neurotoxicity of methyl n-butylketone, ethyl butylketone (EBK) and n-hexane. Due to the varying concentrations in the mixture, NOAELs cannot be generally established.

According to Elkins (1951), exposure to MEK at and above 300 ppm (900 mg/m^3) resulted in headaches, throat irritation and other symptoms of local irritative effects. However, this information is given without further references and thus cannot be substantiated. In an inadequately documented study involving 10 subjects, slight irritation of the nose and throat was reported at 100 ppm (300 mg/m^3) for 3-5 mins and slight eye irritation at 200 ppm (600 mg/m^3). Exposure to 200 ppm (600 mg/m^3) for 8 working hours was considered tolerable by the 10 individuals (Nelson *et al*., 1943). A test of the appropriateness of this estimate under real exposure conditions has not been described.

A number of studies conducted by Dick *et al*. (1984, 1988, 1989, 1992) with groups of 16 to 25 volunteers showed no significant neurobehavioural changes with exposure to MEK at 200 ppm for 4 hours. Symptoms of irritation were reported in only one of the four studies. Most data in workers relate to combined exposure with other solvents and are therefore inconclusive with respect to MEK exposure alone. Analysis of such data supports the conclusion from animal data, that MEK interacts synergistically with other solvents, particularly n-hexane. Chia *et* al. (1993) conducted psychological tests on 19 workers exposed to mixtures of solvents comprised mainly of MEK at concentrations of 11 to 127 ppm (33 to 381 mg/m^3). The other solvents were cyclohexanone (1-9 ppm), tetrahydrofuran (7-22 ppm) and toluene (2-13 ppm). No dose-response relationships were observed, but the performance of the exposed workers was significantly poorer than that of controls in three of the tests. Headaches, irritation of the eyes and nose, coughing and irritability were reported more frequently by exposed individuals than by controls. The authors noted that exposure levels were underestimated because of extensive skin contact.

Recommendation:

The subchronic inhalation study on rats of Cavender *et al*. (1983) was considered to be the starting point for deriving the 8-hour TWA. An uncertainty factor of 10, applied to the NOAEL of 2500 ppm (7500 mg/m^3) to allow for the absence of long term studies, would result in an exposure level of 250 ppm. Human volunteer studies have indicated no significant adverse effects with single 4-hour exposures to 200 ppm. Combining these two strands of evidence and using preferred numbers, the recommended 8-hour TWA is 200 ppm (300 mg/m^3). Limited data (Elkins, 1951) indicate that a STEL (15 mins) of 300 ppm (900 mg/m^3) is required to limit peaks in exposure that could result in irritative effects.

A “skin” notation is required as dermal absorption could contribute substantially to the total body burden.

It should be noted that the recommended limit value does not reflect the possible potentiating effect of MEK in combined exposure with other solvents.

At the level recommended no measurement difficulties are foreseen.

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For 2-butanone (methyl ethyl ketone, MEK) an OEL of 200 ppm (STEL: 300 ppm) has been recommended by SCOEL, based on both local irritation effects in humans and systemic subchronic toxicity in experimental animals (rats). An additional “skin” classification was recommended, which raises the question of applicability of biological monitoring procedures and of setting a BLV.

Metabolism

2-Butanone is taken up predominantly via inhalation. It is also able to enter the body in considerable amounts via the intact skin (21). Approx. 25 % of the 2-butanone taken up by the body is eliminated unchanged by exhalation (l). A minor portion is excreted unchanged in the urine, the rest of is metabolised. Some is oxidised to 3-hydroxy-2-butanone, which has been identified in the urine of exposed workers. Together with the 3-hydroxy-2-butanone the amount of 2-butanone excreted in the urine accounts for only approx. 0.1 % of the dose taken in (2). Further biodegradation to other metabolites, such as acetate and carbon dioxide, has been suggested (2). In experimental animals, apart from the 3-hydroxy-2-butanone, 2,3-butanediol and 2-butanol were identified as products of 2-butanone metabolism (3). It is likely that these metabolites are also formed in the human organism. The alcohols are partially conjugated to sulphate or glucuronic acid.

2-Butanone accumulates in blood compared to ambient air. Perbellini et al. (2) reported that blood concentrations of 2-butanone in steady-state are approx. 35 times higher than those in the ambient air, but the ratio of the 2-butanone concentration in urine to that of ambient air was only 1/4.8. The excretion of 2-butanone in urine follows its level in the blood. Four hours after the start of exposure the 2-butanone concentration in urine reaches steady-state values, which after continuing exposure increase only insignificantly.

Health effects

Although 2-butanone is a frequently used solvent there is only limited knowledge about systemic effects in man. Irritating effects on the eyes and mucous membranes prevent the uptake of higher doses. The odour threshold of 2-butanone is about 25 ppm (5). 2-Butanone concentrations above the OEL of 200 ppm cause irritation of the eyes, as well as of mucous membranes, nose and throat (6). With ambient air concentrations of more than 300 ppm central depressive effects of 2-butanone come to the fore. Also, with such concentrations headache (7) and "stomach ache" (8) have been reported

Whether 2-butanone has

Whether Selection of the biological indicator

2-Butanone is sufficiently hydrophilic to be excreted in the urine to some extent (v.s.). As has been shown in various field studies, there is a dose-relationship between 2-butanone concentrations in the air at the workplace and the 2-butanone excretion in

urine. This makes the 2-butanone concentration in urine fundamentally a suitable parameter for the estimation of internal exposure.

In essence, practical and analytical reasons speak in favour of the 2-butanone concentration in the urine as a parameter for the estimation of internal exposure. The determination of 2-butanone in urine is analytically and diagnostically specific which has led to sufficient literature data on 2-butanone concentrations in urine for the evaluation of a BLV. The determination of 2-butanone in urine can be carried out simply and reliably by means of gas chromatographic head-space analysis (16, 17, 18).

Occupational field studies

The present OEL, as recommended by SCOEL, is 200 ppm. Central nervous effects occur with still higher ambient air concentrations (300 ppm and more). After exposure to concentrations below 200 ppm (corresponding to 590 mg/m3) no adverse effects of 2-butanone on the health of employees have been observed. The evaluation of a BLV value for the 2-butanone excretion in urine is possible via the relationship between external exposure, internal exposure and effect. Such assessments have been documented by DFG (Germany, dated 1988; Angerer, ref. 21) and ACGIH (USA, dated 2000; ACGIH, ref. 22). Both of these committees have reviewed the existing literature at that time, and both have pointed to substantial differences between individual investigations, which were also a main reason for discrepancy in the final recommendations (DFG, recommending a BAT value of 5 mg/l urine; ACGIH, recommending a BEI value of 2 mg/l urine). In the meantime, further field studies have become available, which were assessed, together with the earlier studies, by Imbriani and Ghittori (23). The following is based on this most recent assessment.

Miyasaka et al. (16) studied a group of 62 male workers exposed to 2-butanone. Their inhalation exposure was below 100 ppm. There was a linear relationship between degree of exposure and 2-butanone excretion in urine collected at the end of shift [Cu (µg/l) = 53.0 + 26.3 Ci (ppm); Cu: urinary concentration, Ci: inhaled concentration of 2-butanone]. According to this equation, a urinary 2-butanone concentration of 5.3 mg/l would result from an external exposure to 200 ppm.
Perbellini et al. (24) studied a group of 27 workers exposed to a mixture of 2-butanone, cyclohexane, and acetone during an 8-h work shift. Mean 2-butanone exposure was 34 ppm (range between 3 ppm and 92 ppm). A linear relationship between exposure and urinary concentration was found [Cu (µg/l) = 196 + 9.4 Ci (ppm)]. According to the equation, the urinary concentration of 2.1 mg/l would result from an exposure to 200 ppm.

Ghittori et al. (25) studied 65 workers exposed to 2-butanone. The relationship between exposure concentrations and urinary concentrations is described by the equation Cu (µg/l) = 320 + 9.4 Ci (ppm). According to the equation, exposure to 200 ppm resulted in a urinary 2-butanone concentration of 2.2 mg/l in urine collected during the first 4 h of exposure.

Imbriani et al. (26) confirmed these results in a further study. Seventy-eight workers occupationally exposed to 2-butanone in the manufacturing of leather suitcases were studied. The correlation between urine concentrations and mean-weighted environmental concentrations in occupationally exposed workers was reported by Cu

(µg/l) = 118 + 11.8 Ci (ppm). According to this equation, a TWA exposure to 200 ppm 2-butanone would result in a urinary excretion at the end of exposure of 2.47 mg/l.

Ong et al. (27) studied 59 workers in printing plants. 2-Butanone TWA exposures were between 5 ppm and 300 ppm. The relationship between the logarithms of exposure concentrations and measured urinary concentrations was described by the equation log Cu (µg/l) = -1.22 + 0.83 log Ci (ppm). According to this equation, an exposure to 200 ppm would result in a urinary 2-butanone concentration of 0.35 mg/l. In the original paper the value reported was, on the contrary, 3.62 mg/l (5.1 mol/l). Imbriani and Ghittori (23) have addressed this discrepancy, which apparently is due to a calculation or printing error. The equivalent of a 200 ppm exposure to 2-butanone, according to this study, appears to be an excretion of 3.62 mg/l.

2-Butanone excretion was studied in 14 Korean workers by Jang et al. (28). In this small group, urinary 2-butanone concentrations of 1.4 mg/l corresponded to an exposure to 200 ppm 2-butanone.

Yoshikava et al. (29) studied the relationship between occupational exposure to 2-butanone and its concentration in urine, in a group of 72 workers in a printing factory. In addition to 2-butanone, toluene, xylene, isopropyl alcohol, and ethyl acetate were detected as the main contaminants in all samples. At the end of the work shift, urine samples were collected to determine the urinary 2-butanone. The concentration of urinary 2-butanone ranged from 0.20 to 8.08 mg/l, with a mean of 1.19 mg/l, and was significantly correlated with TWA concentrations of 2-butanone in the air, with a correlation coefficient of 0.889. From the relationship reported [Cu (µg/l) = -56.0 + 26.0 Ci (ppm)], the 2-butanone concentration in urine, corresponding to the OEL/TWA (200 ppm), was calculated to be 5.1 mg/l.

Kawai et al. (30) studied a group of 27 workers exposed to a mixture of 2-butanone and other solvents. The TWA concentration of each solvent was below the corresponding occupational exposure limit. A linear relationship between exposure and urinary concentration was found [Cu (µg/l) = 36.8 + 33.4 Ci (ppm)]. According to the equation, urinary concentration of 6.7 mg/l would result from an exposure to 200 ppm.

Derivation of a BLV

The total data base of 8 field studies appears generally sufficient to establish a BLV for 2-butanone excretion in the urine. The very low values of the smallest (n=14) Korean study by Jang et al. (28) are in apparent contradiction to those of the other studies, especially to all the studies performed in Japan (Miyasaka et al., Yoshikawa et al., Kawai et al.). This study is therefore not included in the further evaluation of a BLV.

The differences between lower values reported reported in the studies of Perbellini et al. (24), Ghittori et al. and Imbriani et al. were explained by Imbriani and Ghittori (23) in a way that the lower values reported by Perbellini et al. (24), Ghittori et al. (25) and Imbriani et al. (26) were determined during the shift or after 4 h exposure, whilst 2-butanone in urine might not have reached its steady-state level before the fourth hour of exposure (Miysaka et al., 16). This would explain the higher values obtained in those studies where the sampling time was by end of the shift (Miyasaka et al., Ong et al., Yoshikawa et al., Kawai et al.). The equivalent urinary 2-butanone excretions for an

TWA exposure to 200 ppm 2-butanone of in the latter studies were 5.5 , 3.6, 5.1 and 6.7 mg/liter, respectively. Taking this database as a whole, SCOEL recommends a BLV for persons occupationally exposed to 2-butanone2-butanone of

5.0 mg 2-butanone excreted per liter urine.

Sampling time is at the end of a working shift.

Interpretation of data

The urine samples for the determination of the 2-butanone concentration must be collected at the reference sampling time (end of exposure/working shift). Immediately after urine collection, aliquots, as a rule 2 ml, should be pipetted into head-space vials (20 ml) which should then be sealed immediately with a gas-tight Teflon-coated rubber stopper. If this portioning into gas-tight head-space vials does not take place immediately and if the urine is left standing for longer periods after sampling at room temperature, then, due to evaporation of 2-butanone, losses are to be expected. The samples can be transported and stored in these head-space vials. According to available data, three-day storage at room temperature does not lead to errors. Storage of the urine samples for longer periods should take place in the deep-freezer at -l8 °C (21).

The 2-butanone concentration in urine should be stated and evaluated as mass per volume, i.e. in mg/l. Relation to creatinine is not appropriate (16), because apparently 2-butanone excretion follows other mechanisms than those for creatinine. According to data from the same authors a relation of the mass of the excreted creatinine to the specific weight has not proved useful (21).

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