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Experimental study on the metabolism of triethylamine in man

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ABSTRACT Five healthy volunteers were exposed by inhalation to triethylamine (TEA; four or eight hours at about 10, 20, 35, and 50 mg/m^3), a compound widely used as a curing agent in polyurethane systems. Analysis of plasma and urine showed that an average of 24% of the TEA was biotransformed into triethylamine-N-oxide (TEAO) but with a wide interindividual variation (15–36%). The TEA and TEAO were quantitatively eliminated in the urine. The plasma and urinary concentrations of TEA and TEAO decreased rapidly after the end of exposure (average half time of TEA was 3·2 h). There was an excellent association between air levels of TEA and the urinary concentrations in samples obtained within two hours of the end of exposure. Thus the urinary level of TEA taken in this period is useful as a biological monitoring of exposure. An air concentration of 10 mg/m^3 corresponds to an average urinary concentration of about 40 mmol/mol creatinine (at sedentary work).

Different species of aliphatic and alicyclic amines, among them triethylamine (TEA), are widely used as catalysts for polymerisation reactions (in urethane and epoxy resin systems) and as solvents and corrosion inhibitors. They are also used as intermediates in the production of various chemicals, including pharmaceuticals.

Exposure to many of these amines may cause adverse health effects such as asthma.[1] Some, TEA,[2,3] and N-methylmorpholine,[1] for example, may cause visual disturbances.[2,3]

The metabolism of TEA has not been studied although this knowledge is important for the use of biological monitoring as a means to control exposure and risk. The metabolism of a similar amine, trimethylamine (TMA), has been studied extensively, both in animals and in man.[4] TMA is, to some extent, excreted unmetabolised in the urine. In addition, trimethylamine-N-oxide (TMAO),[5] is formed which is excreted into the urine. In man a considerable interindividual variation of this oxygenation capacity has been shown.[6] There is an inborn error of metabolism, the "fish odour syndrome," which is due to a deficiency of liver amine oxidase, the lack of which reduces the capacity to oxidise the TMA formed from choline ingested in fish, which in turn results in an increased excretion of TMA in urine, which gives rise to a characteristic smell.[7]

We report here data from people experimentally exposed, by inhalation, to TEA concentrations corresponding to those prevalent in industry.

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Subjects

Five healthy male volunteers aged 46–52 (mean 49) were studied. Their body weight ranged from 78 to 84 (mean 82) kg, and their height from 1·75 to 1·84 (mean 1·81) m. They were normal as regards serum concentrations of amino transferases (ALAT and ASAT) and gammaglutamyl transferase (GT), creatinine, and albumin, and had normal albumin/creatinine and no increase of albumin or glucose excretion in urine.

Methods

EXPOSURE CHAMBER

The exposure chamber has been described earlier.[2] TEA vapour was administered to the air stream entering the chamber and the concentration in the chamber was continuously monitored by infrared spectrometry and at intervals by air sampling. The amine level in the chamber was stable, with a deviation of less than 4% from the target value.

EXPOSURE PROTOCOL

Each individual was exposed on different occasions to air concentrations of TEA in the chamber of about 10(8·9–9·9) and 20(18·5–20·2) mg/m^3. The exposure lasted eight hours. In addition, two subjects were exposed to 34 mg/m^3, and one to 53 mg/m^3, for four hours. Urine was sampled at the start of exposure and then for periods of two hours during the exposure period, during four successive two hour periods after the end of exposure, and then during an additional seven hours, and at least during two additional four hour periods. On four occasions, venous blood was sampled during exposure, as well as one and two to three hours after the end of exposure.

In one subject, at two different exposure concentrations, expiratory air was sampled during the final 10 minutes of each two hour exposure period and one and two hours after the end of exposure.

Expired air was collected with a Douglas bag from all subjects while sitting in the chamber (reading) to determine the respiratory rate.

VISUAL DISTURBANCES

Subjective perceptions of visual disturbances ("foggy vision", "blue haze")[2 3] were registered during the experiment.

ANALYSES

Air samples

The sampling was performed in impinger vessels containing 10 ml 0·1 M hydrochloric acid (HCl) by use of a pump (MSA, 1 l/min). A 2 ml aliquot was added with 2 ml diethylether and 1 ml 5 M potassium hydroxide (KOH), containing 0·25% ammonia (NH_3), shaken and centrifuged at (10 minutes at 1500 g). From the ether phase, a 2 μl at aliquot was injected into a gas liquid chromatograph (GLC; Varian 3700; injector temperature 170°C; stainless steel column, length 2 m, Carbovax 4000 special, and 2% KOH on Chrom W AW, column temperature 70°C; TSD detector, temperature 190°C; evaluation by Hewlett-Packard integrator). For a 15 l sample, the detection limit of the GLC method was 0·01 mg/m^3.

Biological samples

Urine was kept (outside the chamber) in polyethylene bottles and acidified with concentrated HCl (2 ml per 100 of urine). The samples were kept at 4°C until analysis. The stability of urine samples with respect to TEA and triethylamine-N-oxide (TEAO) was excellent; no loss of TEA or TEAO was found at storage at 25°C with or without additions for three weeks and not in acidified samples stored at 4°C for one year. Spiked urine samples (0·88 mmol TEA/l and 0·25 mmol TEAO/l) showed no decrease when analysed with urine samples from the exposure chamber experiments during a four month period.

Creatinine was analysed spectrophotometrically.[6]

The TEA analyses were performed as described above for air samples, with one deviation; the 2 ml urine samples were initially diluted with 4 ml deionised water (in order to obtain the same volume as in analyses of TEAO, see below). The levels were evaluated by use of a urine standard. The detection level was 0·1 µmol TEA/l urine. The precision was 1% of TEA concentrations of 0·5 mmol/l. The accuracy was checked by GLC/mass fragmentography and was found to be good. All samples were run in duplicate.

TEAO was analysed as the difference of TEA before and after reduction. Two ml urine aliquots were added with 1 ml concentrated HCl and 200 mg tin powder and heated for one hour at 95°C. After cooling in ice water, 2 ml ether and 4 ml 4 M KOH was (cautiously) added. Then the same procedure was followed as for TEA. The detection limit was about 0·1 µmol TEAO/l urine. The precision was 6% at calculated TEAO concentrations of 0·13 mmol/l.

The sample used for calculating TEAO was always in the same run as the corresponding TEA sample. All results are based on means of duplicate analyses.

Plasma

Twenty ml of venous blood was taken (outside the chamber) into heparinised tubes and the plasma was separated after 0·5 h by centrifugation at 1500 g for 15 minutes. The samples were divided in 2 ml aliquots, acidified (0·5 ml 1 M HCl), and stored at 4°C until analysis. Determinations of TEA and TEAO were performed as for urine. Detection limits and precisions were the same as in urine.

Expired air

Exhaled air was collected into a Douglas bag, the volumes were determined, the air was bubbled through an impinger vessel, and the TEA content was determined as described above. The valve and the bag were separately washed with 100 ml 0·1 M HCl, which was analysed for TEA. Of the total exhaled amount, an average of 5% was present in the air, 48% in the valve, and 47% on the walls of the bag. Negligible amounts of TEA were found in valve and bag at a second washing.

Results

VISUAL DISTURBANCES

The subject who was exposed to a TEA air level of 53 mg for four hours developed visual symptoms (blue haze), as did both subjects exposed to 35 mg/m^3 for four hours and four of the five subjects exposed to 20 mg/m^3 for eight hours. None had such symptoms at 10 mg/m^3 for eight hours.

Table 1 *Excretion of triethylamine (TEA) and triethylamine-N-oxide (TEAO) at exposure to different TEA air concentrations*

			Urinary concentrations of TEA (and TEAO) during period								
	Exposure		Exposure period (h)				Postexposure period (h)				
Subject No	Level (mg/m³)	Time (h)	0–2	2–4	4–6	6–8	0–2	2–4	4–6	6–8	8–32
			(mmol/mol creatinine)				(mmol/mol creatinine)				
1	9·9	8	8·9 (2·6)	26 (11)	53 (19)	59 (20)	39 (23)	26 (16)	18 (11)	12 (6·7)	2·2 (1·7)
	20·1	8	23 (5·3)	52 (26)	77 (35)	95 (42)	80 (49)	47 (35)	26 (20)	23 (13)	4·1 (3·8)
2	8·9	8	7·3 (0·1)	15 (2·0)	27 (3·1)	40 (5·2)	41 (6·7)	36 (7·0)	24 (5·2)	18 (3·9)	4·0 (1·1)
	20·2	8	13 (1·2)	47 (4·1)	78 (8·7)	79 (16)	89 (12)	68 (13)	51 (11)	37 (7·5)	63 (2·4)
3	9·1	8	11 (1·3)	26 (8·5)	40 (12)	52 (13)	43 (15)	25 (12)	17 (7·5)	9·1 (5·3)	1·2 (0·8)
	18·5	8	17 (2·7)	45 (11)	69 (19)	75 (19)	76 (29)	51 (20)	31 (14)	18 (9·8)	4·9 (2·7)
	35	4	†(†)	44 (12)‡	*(*)	*(*)	73 (30)	59 (23)	30 (15)	20 (11)	6·4 (4·5)
4	9·1	8	11 (0·5)	33 (2·9)	35 (2·9)	54 (9·1)	44 (9·2)	26 (8·1)	14 (4·9)	8·0 (2·6)	2·2 (1·1)
	18·5	8	12 (1·3)	38 (8·4)	59 (13)	110 (24)	79 (21)	55 (18)	32 (12)	22 (7·9)	4·0 (1·5)
	35	4	†(†)	57 (9·2)‡	*(*)	*(*)	72 (26)	61 (20)	53 (9·6)	34 (8·6)	7·7 (3·0)
	53	4	56 (1·4)	195 (22)‡	*(*)	*(*)	153 (33)	112 (37)	62 (19)	30 (14)	7·1 (3·9)
5	8·9	8	10 (0·9)	25 (5·0)	34 (7·6)	47 (8·6)	31 (13)	23 (11)	15 (7·3)	7·4 (4·0)	3·0 (1·6)
	20·2	8	17 (1·5)	60 (12)	76 (19)	76 (24)	72 (26)	38 (19)	27 (15)	19 (7·8)	4·3 (2·9)

*Data not applicable.
†Data not available.
‡Exposure period 0–4 hours.

METABOLISM OF TEA

TEA or TEAO was never detected in urine or plasma samples obtained before the onset of exposure.

During an eight hour exposure, the urinary concentration of TEA (U-TEA) was increased in the two hour period after onset of exposure, at exposure of 20 (fig 1) and 10 (fig 2) mg/m³ (table 1). A continuous further increase followed and a steady state was not reached during the exposure as there was an increase between the 4–6 hour and the 6–8 hour samples. One subject (No 2) showed an increase of U-TEA at both 20 and 10 mg/m³ 0–2 hours after exposure. Another subject (No 3) displayed a corresponding increase in the 20 mg/m³, but a decrease in his 10 mg/m³, experiment. In the other six experiments in three subjects there was a decrease.

Later on, U-TEA decreased (figs 1 and 2; table 1). During the 23–32 hours surveyed after the end of exposure, nobody reached the detection limit. The half lives of TEA excretion in urine after end of exposure at 10 mg/m³ averaged 3·1 (range 2·7–3·6) hours, and at 20 mg/m³, 3·4(2·5–4·5) hours. The fits to the exponential decay curves were good.

The TEAO concentration in urine (U-TEAO) also increased in the 0–2 hour exposure samples and further in the 4–6 and 6–8 hour samples (figs 1 and 2; table 1). During 0–2 hours after end of exposure, there was a decrease of U-TEAO in only two samples (subjects Nos 2 and 4, at 20 mg/m³), whereas there was an increase in all the other eight samples. The behaviour of U-TEA after the end of exposure differed from that of U-TEAO ($p = 0{\cdot}02$, two tailed, sign test). Later on (2–4 h), there was a decrease of U-TEAO in all but one experiment (subject No 2, 10 mg/m³). Nobody reached the detection limit during the 22–32 hour period. The pattern of elimination of TEAO after the end of exposure was similar to that of TEA.

The plasma concentrations of TEA (P-TEA; figs 1 and 2; table 2) increased in the four hour exposure sample on the four occasions studied (in three subjects). There was a further increase in the eight hour samples. One hour after the end of exposure, P-TEA decreased in all experiments. The concentrations were still well above the dectection limit after 2–3 hours in all experiments.

The plasma concentration of TEAO (P-TEAO; figs

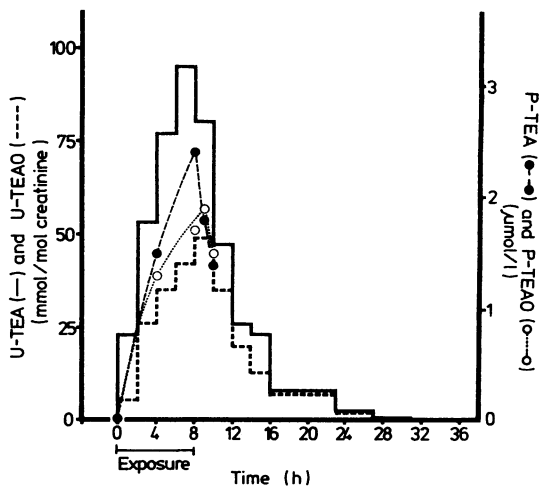

Fig 1 *Urine (U-) and plasma (P-) concentrations of triethylamine (TEA) and triethylamine-N-oxide (TEAO) in subject No 1 at exposure to an air TEA concentration of 20·1 mg/m³.*

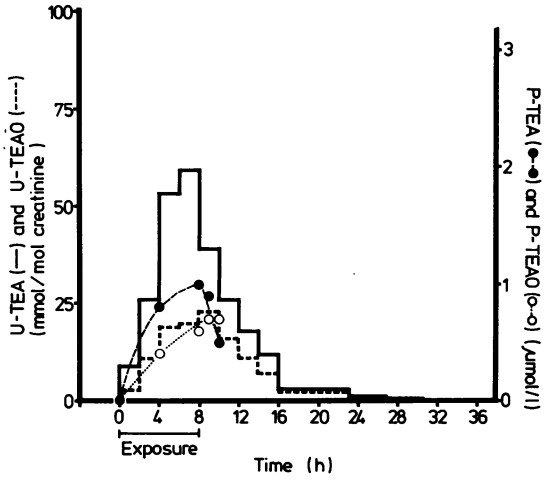

Fig 2 *Urine (U-) and plasma (P-) concentrations of triethylamine (TEA) and triethylamine-N-oxide (TEAO) in subject No 1 at exposure to an air TEA concentration of 9·9 mg/m³.*

1 and 2; table 2) also increased in the four hour and eight hour exposure samples, and further in three of four of the one hour post exposure samples; the other was unchanged. After two to three hours there was a decrease in all but one sample (fig 1).

Using the respiratory rate in combination with the air TEA concentrations,[8] the mean amounts of inhaled TEA were calculated. In the 20 mg/m³ experiments the average was 929 μmol, in the 10 mg/m³ experiments 433 μmol (table 3). The corresponding mean amounts of U-TEA were 655 and 337 μmol during the exposure period and 23–32 hours after. The amounts of U-TEAO were 219 and 103 μmol. The TEA and TEAO excreted in urine corresponds to an average of 97% (range 81–117) of the calculated inhaled amount of TEA. There was no obvious difference between the individuals or between the different air concentrations.

TEAO corresponded to an average of 24% (range 15–36) of the sum of TEA and TEAO excreted in the urine, with no difference between the 10 and 20 mg/m³ experiments. There was, however, a systematic difference between the individuals; the percentage of TEAO at one air concentration was associated with the one at the other (fig 3; r = 0·96, p = 0·001).

In subject No 1 the exhalation of TEA was measured. The concentration before exposure was below the detection limit. Measurements were also made during the final 10 minutes in each two hour period of exposure. At an air TEA concentration of 20·1 mg/m³, the level in exhaled air was 3·6–4·2 mg/m³ (18–21% of the concentration in inhaled air). One hour after end of exposure, the level was 0·2 mg/m³ and two hours after it was 0·1 mg/m³. At an air concentration of 9·9 mg/m³, the concentrations in exhaled air were 1·6–2·2 mg/m³ (18–20% of concentrations in inhaled air). After the end of exposure, the concentrations were 0·2 (1 h) and 0·1 (2 h) mg/m³, respectively.

There was a good correlation between concentrations of TEA in air on the one hand and of either U-TEA + TEAO (Spearman's rank correlation, r_s = 0·95; fig 4), U-TEA (r_s = 0·94), or U-TEAO (r_s = 0·87) in samples obtained 0–2 hours after the end of exposure on the other. The regression line of U-TEA on Air-TEA indicates that a concentration of TEA in air of 10 mg/m³ corresponds to an average U-TEA of 4 mmol/mol creatinine. At that air concentration, the coefficient of variation around the regression line was 14%. The U-TEA in the two subjects exposed to 35 mg/m³ and the one exposed to 53 mg/m³ (not shown in fig 4) fitted well with the regression line, when corrected for shorter exposure time.

Discussion

The occurrence of subjective visual disturbances in most subjects at an exposure of about 20 mg/m³ for eight hours is in agreement with our earlier finding in experimentally exposed subjects,[2] but this toxic concentration is higher than that found in industrial

Table 2 *Plasma concentrations of triethylamine (TEA) and triethylamine-N-oxide (TEAO) at exposure to different TEA air concentrations*

			Plasma concentrations of TEA (and TEAO)					
	Exposure		*Exposure period (h)*		*Postexposure (h)*			
Subject No	*Air level (mg/m³)*	*Time (h)*	*4 (μmol/l)*	*8*	*1 (μmol/l)*	*2*	*3*	
1	9·9	8	0·8 (0·4)	1·0 (0·6)	0·9 (0·7)	0·5 (0·7)	‡	(‡)
	20·1	8	1·5 (1·3)	2·4 (1·7)	1·8 (1·9)	1·4 (1·5)	‡	(‡)
2	20·2	8	1·5 (0·5)	2·6 (0·7)	2·2 (0·9)	‡(‡)	1·1	(0·6)
5	20·2	8	1·4 (0·6)	2·2 (1·0)	1·9 (1·0)	‡(‡)	0·8	(0·9)

‡Data not available

Table 3 *Inhaled triethylamine (TEA) and urinary excretion of TEA and triethylamine-N-oxide (TEAO) at exposure to different TEA air concentrations*

Subject No	Exposure Level (mg/m³)	Exposure Time (h)	Ventilation* (m³)	Inhaled TEA amount (μmol)	Urinary excretion† TEA (μmol)	TEAO (μmol)	TEA + TEAO (μmol)	Urinary TEA + TEAO/ inhaled TEA (%)	Urinary TEAO/ TEA + TEAO (%)
1	9·9	8	4·94	484	263	132	395	82	33
	20·1	8	4·94	983	627	350	977	99	36
2	8·9	8	4·45	392	344	62	406	104	15
	20·2	8	4·45	890	689	125	814	91	15
3	9·1	8	5·02	452	386	141	527	117	27
	18·5	8	5·02	920	674	227	901	98	25
	35	4	2·51	870	568	231	799	92	29
4	9·1	8	4.92	443	398	88	486	110	18
	18·5	8	4·92	901	687	187	874	97	21
	35	4	2·46	852	578	164	742	87	22
	53	4	2·46	1291	1024	239	1263	98	19
5	8·9	8	4·47	394	293	92	385	98	24
	20·2	8	4·47	894	598	207	805	90	26

*During the exposure time.
†During the exposure time and 23–32 hours after.

workers,[3] probably because the latter are, in addition to the average concentration, exposed to brief peak concentrations. The total experience indicates that the time weighted average (TWA) exposure in the workroom should not exceed 10 mg/m³.

The concentrations of TEA in exhaled air are about 20% of those in inhaled air, with no trend during the exposure. This corresponds approximately to the difference between pulmonary ventilation and alveolar ventilation at rest. The exhaled amount corresponds to the fraction of the tidal volume occupied by the dead space. It is thus probable that the absorption of the TEA which reaches the alveolar region is complete. This is in agreement with the extreme water solubility of TEA.

The present data indicate that the major part of the absorbed TEA is excreted in the urine as such. If it is assumed that the absorption of the inhaled amount is 80% (vide supra) the median excretion in different

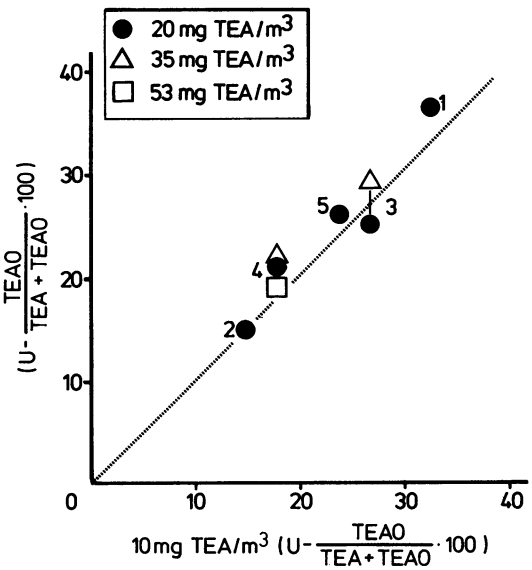

Fig 3 *Fraction (percentage) of sum of triethylamine (TEA) and triethylamine-N-oxide (as TEA equivalents) excreted in urine as TEAO in five volunteers at exposure to air concentrations of TEA of 20 and 10 mg/m³, respectively. Two subjects were exposed to 35 mg/m³ (open circles) as well, one also to 53 mg/m³ (open square). Numbers of subjects are indicated. A line of identity is shown.*

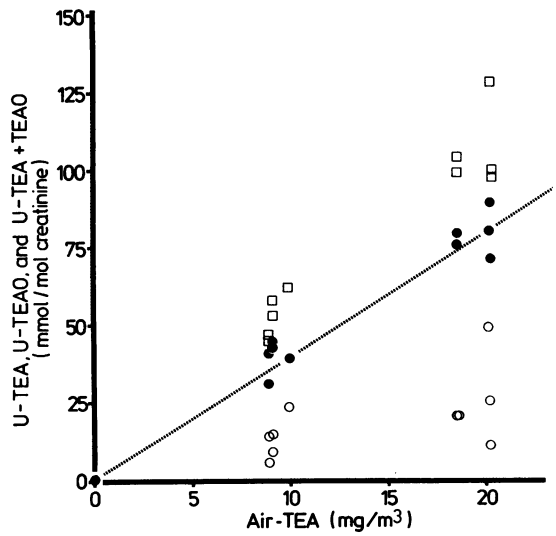

Fig 4 *Relation between concentrations of triethylamine (TEA) in air (Air-TEA) and concentrations of TEA (U-TEA, closed symbols), triethylamine-N-oxide (U-TEAO, open symbols), and sum of TEA and TEAO (U-TEA + TEAO, open squares) in urine samples collected during two hours after end of TEA exposure. The regression line of U-TEA on Air-TEA is shown (Y = 4·0 X + 0·9).*

experiments was 93%. The efficient excretion in urine is not surprising, considering the high water solubility of the compound.

TEAO concentrations were determined after reduction to TEA with a reducing agent. There are several reasons why the TEA obtained in this way really originates from TEAO. Laboratory experiments with TEAO added to pure water solutions and to blank urine have shown that TEAO is completely transformed to TEA with the reducing procedure used. Formation of TEAO may also be inferred by the metabolism of TMA, a similar amine, where TMAO was found as one of the metabolites in people.[5]

The time sequence of the excretion of TEAO indicates that there is a slight time lag in the oxidation.

TEAO formation is probably dependent on a flavin containing mono-oxygenase.[9] It is not clear whether there is any reduction of TEAO into TEA in vivo, as has been shown for TMA in rabbits.[10]

The fractional oxygenation of TEA is much less than that observed for TMA.[11] The transformation was not dependent on the concentration in inhaled air but there was a considerable interindividual variation of TEA transformation, 15 to 36% of the total urinary excretion was present as TEAO in different subjects. This interindividual variation is in accordance with the data on TMA.[6] As the flavin containing monooxygenase is not inducable,[9] the variation is probably genetic. The implication of such a variation has seldom been discussed in industrial toxicology. It may be of great importance at the evaluation of an individual's risk of toxic effect, as well as when analysing the possibiity of biological monitoring of exposure.

The urinary excretion of TEA and TEAO corresponds to more than the total calculated absorbed amount of TEA (median 122%). This is probably due to an error in the estimate of ventilation (hypoventilation) in resting subjects breathing for limited periods into the Douglas bag. Determinations of TEA in exhaled air was only made twice in one subject. The data obtained after the end of exposure do, however, indicate only a minor excretion through this route.

Neither the calculations of absorbed amounts of TEA nor the chromatograms obtained at the analysis of plasma and urine indicated any dealkylation of TEA (formation of diethylamine). Had it been formed, it would appear in the urine, as excretion of diethylamine and monoethylamine has been shown in man after ingestion of these compounds.[12]

Urinary determination is feasible for biological monitoring of TEA exposure. Considering only the interindividual variation in biotransformation of TEA to TEAO, the sum of these two compounds should be used. Nevertheless, taking into account also the greater analytical efforts required in reduction of TEAO and subsequent TEA determination, as compared with TEA analysis only, we recommend the use of TEA alone, which reflects exposure well. It seems that determination of U-TEA, corrected for dilution of urine by use of the creatinine concentration, in urine sampled during the first two hours after the end of work is a useful index. U-TEA in samples obtained during exposure showed a less excellent association with exposure. Also, such sampling involves risk of contamination. Samples of urine voided in the next morning were also inferior, probably because of low concentrations and corrrespondingly greater analytical error.

The present threshold limit value (TLV) for TEA in workroom air in Sweden[13] and the United States[14] is 40 mg/m^3. Assuming a linear relation even outside our area of observations, this should correspond to a U-TEA of about 160 mmol/mol creatinine in resting subjects. Physical work would increase the absorption. Considering the extreme water solubility of the compound, it is probable that the absorption is proportional to ventilation. At moderately heavy work (ventilation 10 cm^3/8h), an Air-TEA of 40 mg/m^3 would then correspond to an U-TEA of 320 mmol/mol creatinine. Data on visual disturbances presented here and earlier,[2 3] however, indicate that 40 mg/m^3 is too high a TLV; 10 mg/m^3 would be more reasonable. This would correspond to an average U-TEA of about 40 mmol/mol creatinine in a resting worker and 80 mmol/mol creatinine in moderately heavy industrial work.

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