HEAC Supplementary Materials – September 4, 2018

TBAC: A technical question was raised about how the route-to-route extrapolation was addressed in the tBAC assessment. The following excerpt is from the draft EPA IRIS tert-butanol assessment and will be discussed at the meeting. An exposure assessment prepared by CARB for TBAC exposure in spray-painting facilities is presented.

From minutes: "Cooper asked Stelljes if the model adjusted for exposure route. Stelljes said to answer that question he would have to see how they did the modeling, and that information is within another document referenced by this one. Keating said he would investigate and bring back that information. He said that most PBPK model extrapolations use continuous exposure and run to steady state, which is not always accurate for occupational exposures"

From Toxicological Review of tert-Butyl Alcohol (tert-Butanol) (CAS No. 75-65-0) June 2017
https://yosemite.epa.gov/sab/sabproduct.nsf/0/8E4436D62DA1FD2D85257E38006A3131/$File/TBA_draft+Tox+Review_Jun2017.pdf

PODs from oral studies – use of PBPK model for route-to-route extrapolation

A PBPK model for tert-butanol in rats has been modified, as described in Appendix B of the Supplemental Information. Using this model, route-to-route extrapolation of the oral BMDLs or LOAEL to derive inhalation PODs was performed as follows. First, the internal dose in the rat at each oral BMDL or LOAEL (assuming oral exposure by a circadian drinking water pattern) was estimated using the PBPK model, to derive an "internal dose BMDL or LOAEL." Then, the inhalation air concentration (assuming continuous exposure) that led to the same internal dose in the rat was estimated using the PBPK model. The resulting POD then was converted to a human equivalent concentration POD (PODHEC) using the methodology previously described in the section, PODs from inhalation studies:

PODHEC = POD (mg/m3) × (interspecies conversion)

= POD (mg/m3) × (481 ÷ 462)

= POD (mg/m3) × (1.04)

A critical decision in the route-to-route extrapolation is selection of the internal dose metric that establishes "equivalent" oral and inhalation exposures. For tert-butanol-induced kidney effects, the two options are the concentration of tert-butanol in blood and the rate of tert-butanol metabolism. Note that using the kidney concentration of tert-butanol will lead to the same route-toroute extrapolation relationship as tert-butanol in blood because the distribution from blood to kidney is independent of route. Data are not available that suggest that metabolites of tert-butanol mediate its renal toxicity. Without evidence that suggests otherwise, tert-butanol is assumed the active toxicological agent. Therefore, the concentration of tert-butanol in blood was selected as the dose metric.

From: Toxicological Review of tert-Butyl Alcohol (tert-Butanol) (CASRN 75-65-0) Supplemental Information June 2017
https://yosemite.epa.gov/sab/sabproduct.nsf/0/8E4436D62DA1FD2D85257E38006A3131/$File/TBA_ERD_SUPPLEMENTAL_INFO_JUN2017.PDF

Appendix B.1.5 Physiologically Based Pharmacokinetic Models

Three physiologically based pharmacokinetic (PBPK) models have been developed specifically for administration of tert-butanol in rats Leavens and Borghoff (2009); Salazar et al. (2015), and Borghoff et al. (2016); other models have incorporated tert-butanol as a submodel following MTBE administration. In Leavens and Borghoff (2009), tert-butanol is incorporated as a metabolite of MTBE; in Salazar et al. (2015) and Borghoff et al. (2016), it is incorporated as a metabolite of ETBE. In all three models, inhalation and oral exposure to tert-butanol can be simulated in rats. A detailed summary of these toxicokinetic models is provided in a separate report evaluating the PK/PBPK modeling of ETBE and tert-butanol (U.S. EPA, 2017).

The PBPK model described in Borghoff et al. (2016), with parameters modified as described by U.S. EPA (2017), was applied to conduct oral-to-inhalation route extrapolation based on an equivalent internal dose (the average concentration of tert-butanol in the blood). The time to reach a consistent periodic pattern of tert-butanol blood concentrations ("periodicity"), given the drinking water ingestion pattern described below, was much shorter than the duration of the oral bioassay studies. To allow for possible metabolic induction, computational scripts used a simulated time of 7 weeks, although periodicity was achieved in only a few days without metabolic induction. The average blood concentration was calculated over the last week of the simulation and was considered representative of the bioassays. To calculate steady state values for continuous inhalation exposure, the simulations were run until the blood concentration had a less than 1% between consecutive days. The continuous inhalation exposure equivalent to a given oral exposure was then selected by identifying the inhalation concentration for which the final (steady-state) blood concentration of tert-butanol matched the average concentration from water ingestion, as described above.

For simulating exposure to drinking water, the consumption was modeled as episodic, based on the pattern of drinking observed in rats (Spiteri, 1982). In particular, rats were assumed to ingest water in pulses or "bouts," which were treated as continuous ingestion, interspersed with periods of no ingestion. During the active dark period (12 hours/day), it was assumed that 80% of total daily ingestion occurs (45-minute bouts with alternating 45-minute periods of other activity). During the relatively inactive light period (12 hours/day), it was assumed that the remaining 20% of daily ingestion occurs; during this time, bouts were assumed to last 30 minutes with 2.5 hours in between. This resulting pattern of drinking water ingestion is thought to be more realistic than assuming continuous 24 hours/day ingestion

PBPK modeling was also used to evaluate a variety of internal dose metrics (daily average TBA blood concentration, daily amount of TBA metabolized in liver, daily average of ETBE blood concentration, and daily amount of ETBE metabolized in liver) to assess their correlation with different endpoints following exposure to ETBE or TBA (Salazar et al., 2015). Administering ETBE either orally or via inhalation achieved similar or higher levels of TBA blood concentrations or TBA metabolic rates as those induced by direct TBA administration. Altogether, the PBPK model-based analysis by Salazar et al. (2015) [which applied a model structurally similar to Borghoff et al. (2016)] indicates that kidney weight, urothelial hyperplasia, and chronic progressive nephropathy (CPN) yield consistent dose-response relationships using TBA blood concentration as the dose metric for both ETBE and TBA studies. For kidney and liver tumors, however, a consistent dose-response pattern was not obtained using any dose metric. These data are consistent with TBA mediating the noncancer kidney effects following ETBE administration, but additional factors besides internal dose are necessary to explain the induction of liver and kidney tumors.

CARB TBAC Exposure Assessment

From: ENVIRONMENTAL IMPACT ASSESSMENT OF TERTIARY-BUTYL ACETATE, CARB, 2006

5.4.1 Method of Evaluation

Indoor concentrations of TBAC were estimated for "personal workspace", "typical" of small and large automotive maintenance facilities. Indoor facility concentrations of TBAC have been calculated in order to estimate the workers' exposures under the assumption that workers will have the greatest exposure to this compound. These analyses utilize information found in existing ARB documents when appropriate.

Exposure in the workplace during a full workday was determined using the 8-hour time-weighted average (TWA) model used in the *Initial Statement of Reasons for Proposed Amendments to the California Regulations for Reducing Volatile Organic Compound Emissions From Consumer Products and Aerosol Coating Products* (ARB, 1996). That model was developed specifically to predict perchloroethylene air concentrations after the use of chemical brake cleaners in automotive repair facilities. Because perchloroethylene is one of the compounds expected to be substituted by TBAC on a pound-per-pound basis, the use of the model is appropriate. The model equation is:

$$C_s = \frac{(24.45 \times 10^{-3}\ m^3/mol)\,(A)(B)(10^6)}{(M)(V)(1 + D)}$$

Where,

C_s = predicted room concentration of TBAC (ppm)

A = TBAC content per can (grams/can), In the 20 oz. can, assuming the 544 grams of perchloroethylene in a can of brake cleaner to be substituted by TBAC on a pound-per-pound basis (ARB, 1996).

B = number of cans used per work period per worker, assumed to be about 0.5 can per day based on the range of 1.0 -1.5 cans used in a work period for the entire facility and an average of 3 workers using such products per facility (Norton, 1993 and ARB, 1996).

M = molecular weight of TBAC = 116.2 grams/mole

V = shop volume, m^3

D = shop air changes/work period

$$\frac{(F)(60\ min/hr)(8\ hr/work\ period)}{H}$$

Where F = air exchange rate, Assumed to be the recommended 1.5 $ft^3/min\text{-}ft^2$. This is also the ASHRAE 62-1989 standard for this type of facility. It should be noted that if the recommended air exchange rate were not maintained in a facility, TBAC levels

would be proportionately higher (ARB, 1996)

H = repair shop ceiling height, 15.6 ft. (ARB, 1996)

10^6 = constant for conversion to parts per million

24.45×10^{-3} = volume of one mole of ideal gas at 25°C and one atmosphere (cubic meter)

5.4.2 Scenarios

Three different scenarios were developed and these are personal workspace (scenario A), small facility (scenario B), and large facility (scenario C). Several inputs/ assumptions were used to estimate indoor concentrations in these three scenarios for the worker when the brake cleaner is used. The worker's workspace air volume, obtained from the previous evaluation, is 27 m^3 for the personal workspace, 1,874 m^3 for the small facility, and 4,733 m^3 for the large facility (ARB, 1996). The air exchange rates per 8-hour work period were assumed to be low according to Norton's study (1993). Specifically, the assumed exchange rates are 18 air changes per work period for personal workspace, 11.5 for both the small facility and the large facility. These inputs/assumptions for each scenario are presented in Table 11.

5.4.3 Results and Conclusions

The results of the evaluation are summarized in Table 11. The use of aerosol brake cleaners with TBAC in automotive maintenance facilities would result in increased air concentrations in the facilities and notably higher personal exposures for the workers, even for facilities with effective exhaust ventilation. This is because the personal workspace scenario does not completely capture the actual "breathing zone" exposure levels of the worker, which could be somewhat higher than the 112 ppm estimated for the area around the worker. The worker's nose and mouth would typically be very close to the directly emitted TBAC, which would represent a higher concentration than the average level in the simulated 27 m^3. However, assuming normal use rates of aerosol brake cleaners and maintenance of the required air exchange rates, the results indicate that the worker's TBAC exposure would not be expected to exceed the current workplace exposure standard. The current California Department of Industrial Relations (Cal-OSHA) Permissible Exposure Limit (PEL) is 200 ppm, or 955 mg/m^3, for an 8-hour time-weighted-average (CCR, 2001). With regard to acute effects, TBAC can cause irritation of the eyes and nose at 200-300 ppm.

The ARB is also concerned regarding the overall (total) exposure of those in the population who would be most exposed to TBAC. To estimate such exposure, the 8-hour workplace exposure level estimated here was combined with the estimated near source exposure levels to estimate a 24-hour time-weighted exposure for those potentially most exposed. For this evaluation, those most exposed to TBAC would be the automotive workers using aerosol brake cleaning products containing TBAC in a small, personal workspace for 8 hours of their 24-hour day, and who live near a large paint booth facility for most of the 16 non-working hours each day. Using the upper estimate of workplace exposure concentration of 532,000 $\mu g/m^3$ (from Table 11) and the

upper estimate of near source concentration of 19.7 $\mu g/m^3$ (from Table 10), and assuming the worker works 8 hours a day for 5 days a week, the calculation would be:

Ave. Total Exposure Conc.

= 5/7 [(8/24) x (Work exposure) + (16/24) x (Non-work exposure)] + 2/7 [19.7]

= 5/7 [(8/24) x 532,000 + (16/24) x 19.7] + 8.15

= 126684 $\mu g/m^3$, or about 127,000 $\mu g/m^3$

Thus, members of the most exposed group, workers who also live near a TBAC source, would be exposed to an average daily exposure of about 127,000 $\mu g/m^3$.

Table 11. Summary of Indoor Exposure Evaluation Results

		Scenario A Personal Workspace	Scenario B Small Facility	Scenario C Large Facility
Results – Predicted air Concentration of TBAC	ppm $\mu g/m^3$	112 532,000	7.3 35,000	2.9 14,000
Inputs				
ppm conversion factor		10^6	10^6	10^6
ppm factor for 25°C and 1 atm		24.45×10^{-3}	24.45×10^{-3}	24.45×10^{-3}
TBAC content/can (grams/can)	A	544	544	544
Number of cans used per work Period	B	0.5	1.5	1.5
Molecular weight of TBAC (gram/mol)	M	116.2	116.2	116.2
Shop volume (cubic meters)	V	27	1874	4733
Shop air changes/work period (25% of typical)	D	18	11.5	11.5
Air exchange rate (cubic feet per minute per square foot)	F	1.5	1.5	1.5
Repair shop ceiling height (feet)	H	10.0	15.6	15.6

MIBK

From minutes: "Harrison said the way exposures often occur is intermittent; continuous occupational exposures are rare. So it is probably more likely that someone is going to pay more attention to the STEL because they are using the chemical for a short duration task. Are there data relevant to the setting of STELS; here we are discussing developmental effects at the proposed PEL level? Are there any data showing use of this kind of solvent for repeated short 10 minute exposures with 40 ppm peaks."

Species (Sex)	Exposure Schedule	Reported Exposure Levels (HEC exposure levels) (mg/m^3)	NOAEL (HEC NOAEL)[a] (mg/m^3)	LOAEL (HEC LOAEL)[a] (mg/m^3)	Effects at HEC Exposure Levels	Reference
Rat (F)	6 hrs/day, each gd 6-15	0, 1229, 4106, 12,292 (0, 307, 1026, 3073)	4106 (1026)[b]	12,292 (3073)[b]	At 307 and 1026 mg/m^3: No treatment-related effects At 3073 mg/m^3: Maternal effects, reduced body weight and body weight gain, hypoactivity, ataxia, lacrimation. Fetal effects, reduced fetal body weight, delayed skeletal ossification	Tyl et al., 1987
Mouse (F)	6 hrs/day, each gd 6-15	0, 1229, 4106, 12,292 (0, 307, 1026, 3073)	4106 (1026)[b]	12,292 (3073)[b]	At 307 and 1026 mg/m^3: No treatment-related effects At 3073 mg/m^3: Maternal effects, hypoactivity, ataxia, lacrimation. Fetal effects, increased fetal death, reduced fetal body weight, delayed skeletal ossification	Tyl et al., 1987
Rat (NS)	6 hrs/day, 5 days/week, 5 months	0, 6146 (0, 1098)	6146 (1098)	ND	At 1098 mg/m^3: Slight narcosis during exposure	Spencer et al., 1975

[a] HECs were calculated according to EPA guidance (U.S. EPA, 1994b) for category 3 gases by adjusting intermittent exposure levels to a continuous exposure basis (see text) and multiplying the result by a ratio of the animal blood gas partition coefficient for MIBK to the human blood gas partition coefficient as follows:

$$NOAEL_{HEC}\ (mg/m^3) = NOAEL_{ADJ}\ (mg/m^3) \times (H_{b/g})_A/(H_{b/g})_H,$$

where

$NOAEL_{HEC}$ = the NOAEL (or LOAEL) expressed in mg/m^3, dosimetrically adjusted for differences between humans and animals in absorptivity of MIBK into blood,

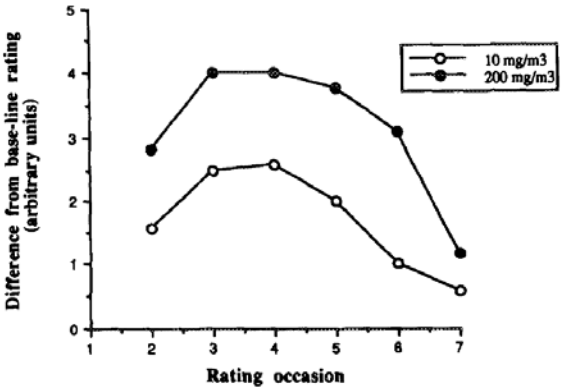
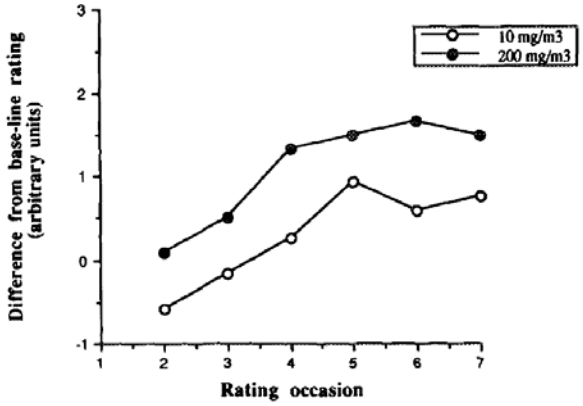
$NOAEL_{ADJ}$ = the NOAEL (or LOAEL) expressed in mg/m^3, adjusted for exposure schedule to estimate equivalent continuous exposure concentration, and

$(H_{b/g})_A/(H_{b/g})_H$ = the ratio of blood:gas partition coefficients of MIBK for the animal value to human value.

EPA guidance (U.S. EPA, 1994b) indicates that the default value of the $(H_{b/g})_A/(H_{b/g})_H$ ratio should be set equal to 1 if blood:air partition coefficient data are not available for either humans or animals. As no animal blood:air partition coefficients were located, the $LOAEL_{HEC}$ and $NOAEL_{HEC}$ values for MIBK were set equal to the continuous duration-adjusted exposure concentrations in all cases.

"Exposure concentrations in the Tyl et al. (1987) developmental toxicity assay were duration-adjusted to derive HEC exposure levels (USEPA, 1994b). This methodology differs from previous EPA practice where the Guidelines for Developmental Toxicity Risk Assessment (USEPA, 1991a) noted that most developmental assessments did not perform dosimetric timing adjustments. This previous science-policy practice had been based on the premise that developmental effects for a number of agents were more likely to depend on peak exposure concentrations. Further evaluation had indicated that developmental effects for a number of agents may be a function of area under the curve of AUC. Hence, in the absence of specific information on the dose-response timing sensitivity for MIBK, EPA has chosen to perform dosimetric adjustment, consistent with public health protection and the science policy set forth in USEPA (2002). In the Tyl study, the daily exposure cycle was comprised of 6 hours of exposure followed by 18 hours of no exposure in rats and mice. Therefore, experimental values in Tyl were duration adjusted by a factor of 6/24 to provide estimated equivalent continuous exposure levels using the equation described in section 4.5.2."

MIBK STEL: Text, figures and data from human subject studies with MIBK. Hjelm is the primary study used in support of the MIBK STEL recommendation. Information from other studies of MIBK irritation cited in the Summary is also presented. These studies used similar approached but did no record symptoms and effects during the exposure (120 minutes).

Gagnon 1994	Four subjects, exposed to 20 and 40 ppm in chamber for 7 hrs	Participants questioned 5 minutes after entering the chamber and then every hour; the final query at 5 minutes prior to exit.	No data presented for reports of irritation and headache. "One person consistently reported eye, nose or throat irritation as well as headache. Eye and throat irritation was reported once each among the other subjects. Headache was reported frequently by a second person, while no one reported feelings of nausea."
Iregren, 1993	Six males, 6 females "Control" 2.5 ppm Exposed; 50 ppm; 2-hours; first 90 minutes with exercise, 30 rest;	Irritation and CNS symptoms was evaluated using the SPES questionnaire. Symptoms assessed every 30 min during exposure (0, 30, 60, 90 (end exercise), 120 (end exposure), 150 and 180 min. Symptoms were evaluated as differences from baseline ratings and the two-way ANOVA was performed with exposure level and measurement location as sources of variation. Symptoms of irritation were not significantly different between the two exposure levels; they varied over measurement occasion ($F_{5, 55} = 8.5$; $p \leq 0.001$). The occurrence and/or intensity of the CNS symptoms increased with exposure ($F_{1, 11} = 5.2$; $p \leq 0.001$) and with repeated measurement ($F_{5,55} = 4.9$; $p \leq 0.001$).	**Symptoms and irritation**  **CNS effect** 
Dick 1992	17 subjects; 100 ppm; Control exposure consisted of a 5-min, 25 ppm MEK-MIBK presented at the beginning of 2-hr exposure period.	Subjective questionnaire used "yes/no" format. The items reported were: (1) presence of odor; (2) strong odor; (3) objectionable odor; (4) headache; (5) nausea; (6) throat dryness or coughing; (7) tearing; and (8) unpleasant exposure.	"Tables 6 and 7 present the significant probabilities for the large number of measurements taken on the subjects. Examination of these tables reveals few significant probabilities that represent neurobehavioral decrements in the chemical-exposure groups. Of the 72 probabilities (18 ANOVAs and 54 regression coefficients), only six significant differences were found for the chemical-exposure conditions (i.e., near the level expected by chance). The results of the questionnaire showed that self-reported sensory and irritant effects varied across the experimental conditions. The only statistically significant effect found between control and exposed subjects was for the presence of strong odor. Approximately 20-30% of the subjects exposed to MIBK reported sensory and irritant effects (i.e., odor, headache, nausea, throat irritation, tearing). These percentage results agree with Hjelm (1990), who exposed subjects either to 10, 25, or 50 ppm MIBK with 50 W exercise and used a similar dichotomous choice (i.e., yes/no) questionnaire to assess sensory and irritant effects."

Hjelm, Int Arch Occup Environ Health (1990) 62:19-26

NOTES: 10/100/200 mg/m³ MIBK = 2.5/25/50 ppm.

Symbols represent time points during and after exposure when questionnaires were administered.

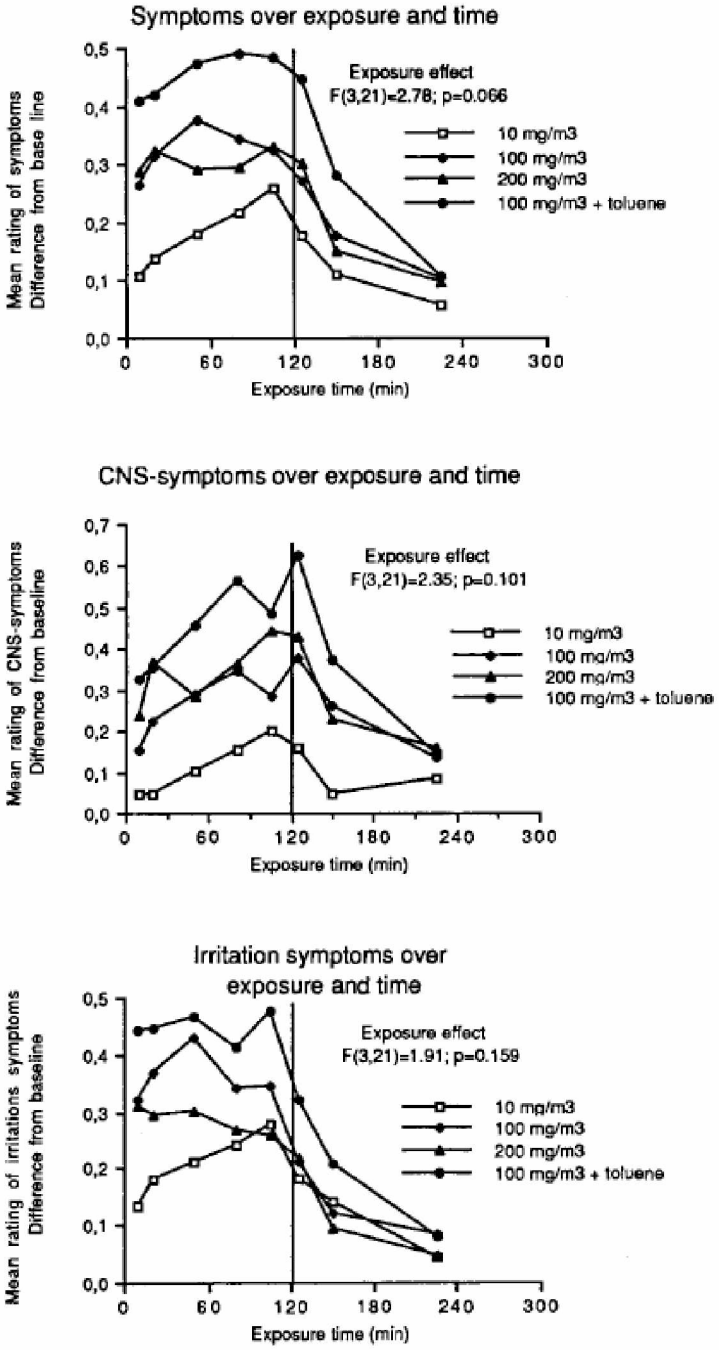


Fig. 5a, b, c. Symptom indices over exposure and time at three different exposure levels of MIBK and a combination of MIBK and toluene (2 h, 50 W). The indices are expressed as the mean of the differences between the ratings at each occasion and the baseline measurement. Mean values of eight persons are given.

Occurrence of irritative and CNS symptoms. Two symptom scales were used in this study. The subjects answered one questionnaire with yes/no alternatives concerning acute symptoms. The symptoms asked for were irritation in the eyes, nose and throat, in addition to CNS symptoms such as headache, nausea and vertigo. The subjects answered the questionnaire before and at five times during exposure.

The other acute symptoms questionnaire, SPES32, from the Swedish Performance Evaluation System (SPES) (Gamberale et al. 1988), contains 17 items regarding symptoms from the CNS as well as symptoms of local irritation. The subjects are asked to rate the present intensity of each symptom on a six point scale. This questionnaire was administered on nine occasions, with the first rating immediately before onset of exposure, and the last rating almost 2 h after the subject left the exposure chamber.

Statistical evaluation. The SPES scale Acute symptom was evaluated with respect to three different indices. The first index was the mean rating for all the items, the second was based solely on symptoms from the CNS, and the third index was concerned with items regarding local irritation (see Iregren 1986). The indices were computed as the mean of the differences between the rating on each occasion and the rating at the measurement before onset of exposure. The Mood scale was evaluated in the same way, although with respect to two subscales only, Stress and Activity.

Table 2. The number of subjects out of the 8 participating with symptoms (yes/no alternatives at any point during the exposure) versus exposure level. Any pre-exposure symptoms persisting during exposure are not included

Symptom	Exposure concentration of MIBK, mg/m³			
	10	100	200	100 + toluene
Irritation in the eyes	1	1	0	0
Irritation in the nose	1	3	3	2
Irritation in the throat	1	3	3	0
Headache	0	2	2	3
Nausea	0	0	1	1
Vertigo	1	2	2	3

CONCLUSION: Changes in irritation and CNS symptoms were observed after exposure to 2.5, 25, and 50 ppm MIBK. The x-axis is time and shows two measures within the first 15 min of the 120 min exposure. The y-axis the mean of the difference in the reported symptoms and baseline response before exposure for the 8 individuals. Standard deviations not reported. Table 2 show the data used for the top figure – acute symptoms. No more than 3 of 8 subjects report symptoms at any concentration. There was high intraindividual variability in the SPES results for half of the subjects.