Turpentine Substance Summary

Summary

An 8-hour PEL for turpentine (CAS number 8006642) and selected monoterpenes (alpha-pinene, beta-pinene, and delta-carene, CAS numbers 80568, 127913, 13466789 respectively) of 20 PPM is proposed for discussion.

Physical Properties

Substance Name: turpentine

CAS Number: 8006-64-2 MW: 136 g/mole

Synonyms: gumspirits, gum turpentine, spirits of turpentine, steam distilled turpentine, sulfate wood turpentine, turps, wood turpentine

Molecular formula: $C_{10}H_{16}$ (approx)

Conversion factors at 25 °C and 760 mm Hg: 1 ppm = 5.6 mg/m^3

Physical Properties:

Physical Description: colorless liquid with a characteristic odor

Boiling Point: 150 to 180 °C

Melting Point: -60 to -40 °C

Vapor Pressure: 1.9 to 5 mm Hg (0.25 to 0.67 kPa) at 20 °C

Specific Gravity: 0.86

Solubility: insoluble in water, soluble in alcohol, ether, chloroform, and glacial acetic acid

Odor Threshold: 100 to 200 ppm

Flammability and Other Hazards:

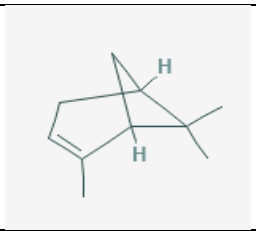
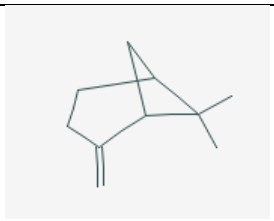
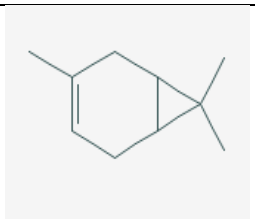
Flash Point: 32.2 to 46.1°C (closed cup)

Lower Explosive Limit: 0.8%

Composition:

The chemical composition of turpentine can vary with the source and method of derivation. Chemical and physical properties for selected monoterpenes are presented below. The ratio of the three monoterpene constituents in turpentine is approximately 10:1:5, α–pinene: β–pinene: 3-carene.

Table 1. Chemical and Physical Properties for Selected Monoterpenes

	α–Pinene	β–Pinene	3-Carene
CAS Number	80-56-8	127-91-3	13466-78-9
Structure			
Molecular Weight	136.24	136.23	136.23
Melting Point	-55 °C	-61.5 °C	< 25 °C
Boiling Point	155 to 156 °C	168 to 169 °C	168 to 169 °C
Vapor Pressure	4.75 mm Hg at 25 °C	2.93 mm Hg at 25 °C	3.72 mm Hg at 25 °C
Solubility	Insoluble in water; soluble in most organic solvents	Insoluble in water; mixes with grease, organic solvents, and oils	Insoluble in water; mixes with grease, organic solvents, and oils
Special Characteristics			Readily oxidizes in air

Uses & Applications

Turpentine is produced as a by-product in the paper and pulp industry. Turpentine and its monoterpenes are used as a solvent for surface coatings, liniments, perfumes, and as an intermediate in the synthesis of camphor and menthol. It is also used in veterinary practice as expectorant, rubifacient, and antiseptic. It is used less as a paint thinner since the 1940s. (ACGIH, 2014) Pinene and carene have been found in cannabis operations (NIOSH, 2018).

Occupational Exposure Limits (OELs) and Other Recommendations

Table 2. Select OELs

Source and Date	Exposure Limits	Basis/Source/Reference
Cal/OSHA PEL	100 ppm 8h TWA	
Washington LNI (OSHA) PELs	100 PPM 8h TWA, 150 PPM STEL	Irritation
Fed OSHA PEL	100 ppm 8h TWA	
NIOSH IDLH	800 ppm	Acute toxicity data in humans [Lehmann and Flury 1943] and animals [Skramlik 1956; Sperling and Collins 1964]; also 10% of LEL of 0.8% (NIOSH IDLH Table)
NIOSH REL	100 ppm 10h TWA	
ACGIH TLV (2001)^	20 ppm 8h TWA	Lung irritation
MAK (2019)	5 ppm 8h TWA	Systemic effect
HSE WEL	100 ppm 8h TWA, 150 ppm STEL	

^The above OELs apply to turpentine (CAS 8006642) with the exception of the ACGIH TLV which applies to turpentine (CAS 8006642) and selected monoterpenes (CAS 80568, 127913, and 13466789).

Table 3. Summary of Other Recommendations

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA	-	-	-
US EPA	-	-	-
NTP*	-	-	-
ATSDR	-	-	-
IARC	-	-	-

*Toxicity studies of αinene (a main component in turpentine) in both male and female rats and mice by inhalation exposure for 2 weeks and 3 months showed effects on liver, urinary system and male reproductive system (NTP, 2016)

Health Effects

The health effects of turpentine have mostly been characterized in human volunteer exposures and workplace investigations, mostly in the timber, lumber, and wood processing industries. No animal studies are available for the turpentine mixture; there are limited studies of the main constituents, pinene and carene. Controlled human exposures provide the best evidence with which to assess the hazard from turpentine, but have limitations. Most workplace investigations are confounded by the co-exposure to wood dust and other volatile organic compounds. Wood dust has been categorized as a 1A carcinogen by IARC. AOther chemicals used in wood processing such as formaldehyde and phenol have been shown to have greater respiratory and carcinogenic potency than turpentine. Some well-defined workplace studies in the timber and lumber industries do provide insight into the health effects of turpentine.

Respiratory and ocular effects are the predominant acute effects of turpentine. Turpentine is a mucosal irritant and causes inflammation in the nasal and respiratory tracts and ocular irritation. These effects have consistently been documented in workplace symptom surveys however clinical measures of respiratory capacity and biochemical measures of inflammation provide more accurate endpoints to assess the hazard. Turpentine is also an established contact sensitizer and there are anecdotal case reports of respiratory sensitization and asthma in workers. Finally, turpentine has been linked to respiratory cancers from wood dust and leukemia in case-control studies of solvent exposure.

Human Exposure Studies

ACGIH summarized these studies in its recent review of turpentine in 2014 (see Appendix). The key studies generally exposed healthy volunteers to 2, 40, or 80 ppm of pure turpentine or a turpentine constituent for 2 hours during light physical exercise (50W) with significant effects only observed at the highest concentration. In these studies, subjects rated symptoms of irritation and CNS effects, pulmonary functions were measured pre- and post-exposure, and blood and urine

samples were obtained for pharmacokinetic analysis. With α-pinene, reported irritation of eyes, nose and throat was significantly higher ($p<0.002$) than the lower dose groups (Falk, 1990). Mean changes in post-exposure lung function were not statistically significant. Using the same approach with 3-carene (Falk, 1991), there was a statistically significant increase in reported irritation at 80 ppm ($p < 0.05$). There was a non-significant increase in airway resistance ($p=0.20$) at 80 ppm. When these studies were repeated with turpentine (α pinene, β pinene and 3-carene), a significant reduction in airway resistance was experienced only at 80 ppm after 2 hours (Filipsson, 1996). During exposure to turpentine the subjects rated more discomfort of the throat or airways ($F = 5.7$, $P = 0\ 048$) than during exposure to control conditions (10 mg/m3 of 3-carene). The symptom ratings in this study (about 5% of the scale) were similar to those for exposure to 450 mg/m3 of 3-carene. In a more extended chamber study, Johard (1993) exposed 8 volunteers to 80 ppm turpentine (α pinene, β pinene and 3-carene, 10:1:5) for 3 hours on 4 occasions over two weeks with light exercise. Following exposure, bronchoaveolar lavage (BAL), biochemical analysis of BAL fluid and a bronchial challenge test of the test subjects were conducted. BAL and biochemical analysis were performed before and after exposure. After the terpene exposure, there was a significant increase of the total alveolar cell concentration due to an increase in the number of alveolar macrophages. The number of mast cells also increased significantly. The total cell concentration was significantly higher (126×10^6 cells/L, i.q.r. 122-126) than before (76×10^6 cells/L, i.q.r. 61-125); $p < 0.05$). The concentration of the macrophages increased from 72×10^6cells/L (i.q.r. 58-114) to 121×10^6 cells/L (111-156; $p < 0.05$), thus constituting the main part of the increment. The concentrations of the lymphocytes, polymorphonuclear neutrophils, and the eosinophils did not change significantly. However, the number of mast cells increased significantly from 1/10 visual fields (pre-exposure) to 5/10 visual fields ($p < 0.05$). Concentrations of albumin, total fibronectin, native fibronectin, hyaluronan, and tryptase in BAL fluid did not change significantly after exposure. There was no significant change in challenge test results after the exposure. See Appendix for the data tables from the 4 studies.

Using chemicals directly emitted from pinewood panels, no concentration-dependent effects before or after exposure to the emissions were measured with respect to sensory irritation, pulmonary function, exhaled nitrogen oxide, and eye blink frequency in healthy nonsmokers exposed for 2 h. Terpene and aldehyde exposure concentrations ranged from about 3.50 ± 0.51 mg/m^3 and 0.07 ± 0.008 mg/m^3, 5.00 ± 0.95 mg/m^3, and 0.20 ± 0.02 mg/m^3 or 9.51 ± 1.10 mg/m^3 and 0.21 ± 0.04 mg/m^3 (Gminski, 2011).

Several workplace studies have looked at inflammatory markers in workers in sawmill operations. In these studies, there is also exposure to wood dust so the effects of the terpenes are more difficult to distinguish. The concentration of interleukin 6 in nasal lavage fluid and lung function were determined in 19 volunteers stationed in a sawmill for 5 hours with or without respiratory protection in an effort to examine the contribution of the terpene to inflammation (Dahlqvist, 1996). Dust exposures were low: 0.13 mg/m3 without the respirators, 0.04 mg/m3 with, and the two groups were statistically different ($p<0.01$). Respective terpene levels were 52 mg/m3 and 58 mg/m3. Median interleukin-6 concentrations only increased significantly in lavage fluid in subjects without respirators (Figure 1, $p< 0.05$). There were no significant differences in pulmonary function measurements in either group. However, decreases in carbon monoxide diffusion capacity (TLco) and alveolar volume

were significantly and negatively correlated with terpene concentration (correlation: -0.61; p, 0.05) and was pronounced in the group with no respirators (Figure 2).

Figures 1-2: Respiratory measures in woodworkers with and without dust masks. From Dalquivst 1996.

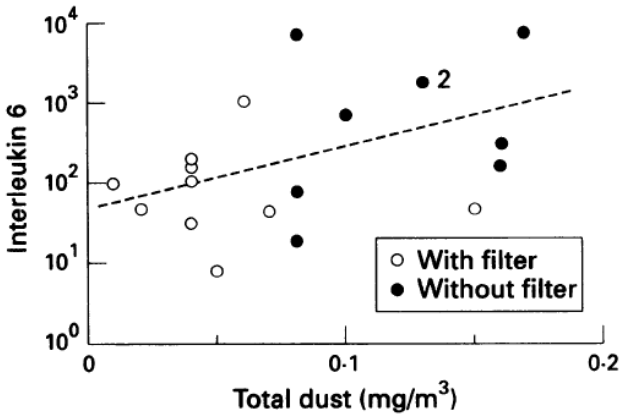


Figure 1 The relation between change in IL-6 in the nasal lavage fluid after exposure as a percentage of the unexposed value (log scale) and time weighted average concentrations of total dust. Values after exposure with and without a particle filter are shown (n = 19, ρ = 0·43, P < 0·05, one tailed test).

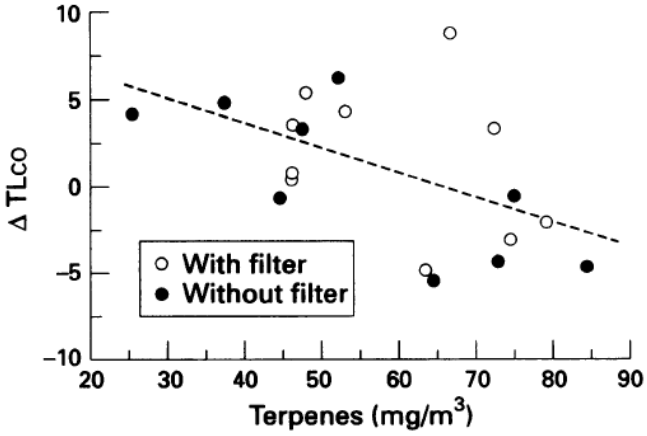


Figure 2 The relation between change in TLCO after exposure and time weighted average concentrations of the sum of terpenes. Values after exposure with and without a particle filter are shown (n = 19, ρ = 0·46, P < 0·05, one tailed test).

A significant reduction in carbon monoxide lung diffusion capacity (p< 0.05) was also observed in 48 sawmill workers with terpene concentrations ranging from 6.5 – 15.3 ppm (GM) and saw dust levels ranging from 0.2 to 0.4 mg/m3 (Eriksson, 1996). No effects on FEV or FVC were observed and eye irritation was the only one of 10 symptoms that increased significantly by the end of the shift. Pre-study FEV1 measures were significantly lower than controls (p< 0.05). This group repeated the study with 39 workers in a wood joinery shop (Eriksson, 1996) with similar terpene levels (GM = 7.8 ppm; wood dust GM = 0.4 mg/m3) and found similar results – no effects on worker lung function at the end of the work shift. However, like the other study, the workers had significantly lower pre-shift lung function values (VC, FEV1 of about -10%) as compared with the local reference values based upon a large cohort of healthy subjects. The lung function results still remained significantly low when smokers and ex-smokers were excluded, and therefore smoking was not the confounding factor. The lung function reduction was more pronounced in terms of airflow (FEV1) than in terms of a possibly restrictive pattern (VC). Consequently, the ratio FEV1/VC was significantly lower for the joinery shop workers than for the reference population and therefore indicated an obstructive lung function pattern. This is an interesting observation since no asthmatics were included in the study, and also manual workers commonly have supernormal lung function values and a "healthy worker effect" is often a confounding factor.

A recent study examined respiratory symptoms in 39 wood pellet (from soft wood) makers exposed to relatively high dust levels (personal samplers: GM = 1.7 [0.16 – 1.9]) but low terpene levels (0.12 – 5.1 ppm) (Lofstedt 2017). While workers reported a higher frequency of nasal symptoms than

controls, there was no statistically significant difference in lung function (vital capacity FEV1 and FEV%) before and after shifts. The subjects with physician-diagnosed asthma had lower VC ($p = 0.052$) and FEV_1 ($p < 0.01$) compared to the other participants.

Animal Studies

Animal studies addressing the general toxicity, reproductive and developmental toxicity, and carcinogenicity of turpentine and the monoterpenes are not available. One historic study of turpentine inhalation in rats at 897 to 1,795 ppm observed no effects (Chapman, 1941). The National Toxicology Program conducted a 3-month sub-chronic inhalation study of α-pinene study in rats and mice (NTP, 2016, see table 4 and abstract below). No chronic animal bioassay of turpentine or the individual monoterpenes have been conducted.

Table 4: NTP, 2016: Findings Considered to be Toxicologically Relevant in Rats and Mice Exposed to α-Pinene by Inhalation for 3 Months

	Male F344/N Rats	**Female F344/N Rats**	**Male B6C3F1/N Mice**	**Female B6C3F1/N Mice**
Concentrations in air	0, 25, 50, 100, 200, or 400 ppm	0, 25, 50, 100, 200, or 400 ppm	0, 25, 50, 100, 200, or 400 ppm	0, 25, 50, 100, 200, or 400 ppm
Survival rates	10/10, 10/10, 10/10, 10/10, 10/10, 10/10	10/10, 10/10, 10/10, 10/10, 10/10, 4/10	10/10, 10/10, 10/10, 10/10, 10/10, 10/10	10/10, 10/10, 10/10, 10/10, 10/10, 10/10
Organ weights	↑ Absolute and relative kidney weights; ↑ Absolute and relative liver weights	↑ Absolute and relative heart weights; ↑ Absolute and relative kidney weights; ↑ Absolute and relative liver weights	↓ Absolute kidney weights; ↑ Absolute and relative liver weights	↑ Absolute and relative liver weights
Reproductive toxicity	↓ Sperm per cauda	None	↓ Sperm per cauda	None
Nonneoplastic effects	Kidney: granular casts (0/10, 9/10, 10/10, 10/10, 10/10, 10/10); hyaline droplet accumulation (1/10, 10/10, 10/10, 10/10, 10/10, 10/10)	None	Urinary bladder: transitional epithelium hyperplasia (0/10, 0/10, 0/10, **7/10, 10/10, 10/10**)	Urinary bladder: transitional epithelium hyperplasia (0/10, 0/10, 0/10, **6/10, 10/10, 10/10**)
Genetic toxicology	Bacterial gene mutations: Negative in *E. coli* with or without S9; negative in *S. typhimurium* strains TA98 and TA100 with or without S9 Micronucleated erythrocytes mouse peripheral blood *in vivo*: Negative in males and females			

NTP, 2016:

> "In the 3-month studies, groups of 10 male and 10 female rats and mice were exposed to α-pinene by whole body inhalation at concentrations of 0, 25, 50, 100, 200, or 400 ppm, 6 hours per day, 5 days per week for 14 weeks. All exposed male rats and male and female mice survived to the end of the studies, while six 400 ppm female rats died before the end of the study The major targets for α-pinene toxicity were the liver, urinary system, and male reproductive system. The absolute liver weights were significantly greater than those of the chamber controls in 400 ppm male rats (13%), male mice (21%), and female mice (18%), and female rats exposed to 50, 100, or 200 ppm (14%, 14%, and 17%, respectively); however, accompanying treatment-related histopathologic lesions did not occur in the liver of male or female rats or mice. Absolute kidney weights were increased in male rats exposed to 100 ppm or greater (up to 25%) and 50 and 200 ppm female rats (10%); in males, these increases were accompanied by histopathologic lesions including granular casts and hyaline droplet accumulation at all exposure concentrations, as well as exposure concentration-dependent increases in the severity of nephropathy, which is a common spontaneous lesion observed in male rats. Exposure concentration-dependent increased incidences of transitional epithelium hyperplasia of the urinary bladder occurred in male and female mice exposed to 100 ppm or greater (males: 100 ppm, 70%; 200 ppm, 100%; 400 ppm, 100%; females: 60%, 100%, 100%). There were also significantly lower numbers of sperm per cauda compared to the chamber controls in 200 and 400 ppm male rats (19%) and 100, 200, and 400 ppm male mice (24%, 33%, and 40%, respectively).
>
> Under the conditions of the 3-month inhalation studies, there were treatment-related lesions in male and female rats and mice. The major targets from α-pinene exposure in rats and mice included the liver, urinary system (kidney of rats and urinary bladder of mice), and cauda epididymal sperm. The most sensitive measures of α-pinene exposure in each species and sex were increased incidences of kidney lesions in male rats [lowest-observed-effect level (LOEL)=25 ppm], increased relative liver weights in female rats (LOEL=25 ppm) without accompanying histopathologic changes, decreased sperm per cauda and increased incidences of transitional epithelium hyperplasia of the urinary bladder in male mice (LOEL=100 ppm), and increased incidences of transitional epithelium hyperplasia of the urinary bladder in female mice (LOEL=100 ppm)."

In the NTP study, there were multiple indications of urinary system injury following α-pinene exposure. In the 2-week and 3-month studies, relative kidney weights were increased in a concentration-dependent manner in male and female rats. In addition, prominent granular casts were observed in the lumens of the renal tubules along the corticomedullary junction. These casts are an indication of previous injury and death of the renal tubule epithelium with accumulation of the cellular debris (casts) in the tubules. There was also evidence of exacerbation of the chronic progressive nephropathy that is a common spontaneous change in the kidneys of male rats as evidenced by a concentration-related increase in the severity of this lesion. The lesions meet some of the criteria used by the United States Environmental Protection Agency (1991) and the International Agency for Research on Cancer (1999) for induction of renal tumors by this mechanism. However, it should be

noted that measures of α2μ-globulin and cell proliferation, which are also criteria used by these agencies, were not performed in the study. While it is possible that the observed kidney lesions are secondary to α2μ-globulin nephropathy, the increases in kidney weights in both male and female rats suggest that another independent mechanism of toxicity may have played a role in the lesion development.

The findings of the sub-chronic study indicate that the urinary system (kidney and bladder) and liver are the two systems most likely to be affected by exposure to α-pinene in rats and mice. While relative liver weights increased, these organ weight changes were not accompanied by histopathologic lesions. Increased liver weight is a common finding in toxicity studies and can be associated with induction of liver metabolizing enzymes. α-Pinene has been shown to increase both phase I and phase II metabolizing enzymes *in vitro* and *in vivo* (NTP, 2016).

The primary effect in mice caused by exposure to α-pinene was an increased incidence of transitional epithelium hyperplasia of the urinary bladder in males and females exposed to 100 ppm or more, the severity of which increased with increasing exposure concentration. This finding is relatively rare among subchronic mouse studies at the NTP. Transitional epithelium hyperplasia in the urinary bladder can be either reparative (e.g., regenerative or reactive) or preneoplastic. Specific histopathologic indicators of either type of hyperplasia (e.g., calculi for reparative, cellular atypia for preneoplastic) were not evident in male or female mice from the current study; therefore, the neoplastic potential of the transitional epithelium hyperplasia of the urinary bladder that did occur is uncertain.

In addition to the urinary system, the male reproductive system may be a target of α-pinene toxicity, with more pronounced effects in mice than in rats (see Table X below. In male rats, absolute sperm per cauda decreased by approximately 20% at the two highest exposure concentrations compared to chamber controls. There was an accompanying minor decrease in epididymal weights that did not reach significance. Therefore, the possibility that the change in absolute sperm per cauda was due to a decrease in epididymal weight cannot be ruled out. In male mice, sperm per mg cauda decreased by 24% and 37% in the 200 and 400 ppm groups, respectively. According to NTP, histopathologic analysis is warranted with decreases of this magnitude; however, none were conducted in the sub-chronic study. NTP concluded that further studies on the effects of α-pinene on reproductive function are warranted. Under the conditions of the 3-month studies in rats and mice, there was no evidence of female reproductive toxicity.

Table 5. Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Inhalation Study of α-Pinene

RAT (10 per group)	Control	100 ppm	200 ppm	400 ppm
Necropsy weights				
Necropsy body wt	335 ± 6	334 ± 7	332 ± 4	322 ± 6
L. Cauda epididymis	0.1973 ± 0.0063	0.1923 ± 0.0062	0.1861 ± 0.0062	0.1802 ± 0.0057
L. Epididymis	0.4860 ± 0.0067	0.4724 ± 0.0094	0.4780 ± 0.0090	0.4650 ± 0.0092

L. Testis	1.4283 ± 0.0257	1.4061 ± 0.0160	1.4001 ± 0.0191	1.4337 ± 0.0213
Spermatid measurements				
Spermatid heads (10^3/mg testis)	129.3 ± 4.2	132.8 ± 3.7	136.7 ± 3.1	137.5 ± 3.3
Spermatid heads (10^6/testis)	167.5 ± 5.6	163.8 ± 5.1	168.3 ± 4.3	172.4 ± 3.5
Epididymal spermatozoal measurements				
Sperm motility (%)	91.73 ± 1.26	91.40 ± 0.93	91.24 ± 0.80	90.93 ± 0.89
Sperm (10^3/mg cauda epididymis)	615.0 ± 34.3	596.5 ± 31.8	526.3 ± 19.0	547.4 ± 14.0
Sperm (10^6/cauda epididymis)	120.89 ± 6.79	113.16 ± 3.11	**97.52 ± 3.51****	**98.40 ± 3.02****
MOUSE (10 per group)				
Necropsy body wt	37.1 ± 0.6	35.9 ± 0.7	35.5 ± 1.0	36.2 ± 0.5
L. Cauda epididymis	0.0217 ± 0.0013	**0.0173 ± 0.0007****	0.0187 ± 0.0010	0.0198 ± 0.0008
L. Epididymis	0.0527 ± 0.0013	0.0503 ± 0.0013	0.0485 ± 0.0019	0.0489 ± 0.0021
L. Testis	0.1144 ± 0.0021	0.1102 ± 0.0026	**0.1068 ± 0.0019***	0.1073 ± 0.0018
Spermatid measurements				
Spermatid heads (10^3/mg testis)	190.9 ± 9.4	197.8 ± 5.9	**214.5 ± 8.1***	202.7 ± 6.4
Spermatid heads (10^6/testis)	19.88 ± 1.09	20.02 ± 0.53	20.75 ± 0.65	19.48 ± 0.58
Epididymal spermatozoal measurements				
Sperm motility (%)	90.25 ± 0.34	88.31 ± 0.86	89.74 ± 0.80	87.95 ± 1.08
Sperm (10^3/mg cauda epididymis)	704.8 ± 64.9	690.7 ± 55.9	**537.5 ± 27.0***	**445.8 ± 13.5****
Sperm (10^6/cauda epididymis)	24.45 ± 0.95	**18.40 ± 0.41****	**16.48 ± 0.72****	**14.64 ± 0.25****

Rat: ** Significantly different (P≤0.01) from the chamber control group by Shirley's test.
Data are presented as mean ± standard error.

Mouse: * Significantly different (P≤0.05) from the chamber control group by Dunnett's test (left testis weights), Dunn's test (spermatid heads/mg testis measurements), or Shirley's test (sperm/mg cauda epididymis measurements). ** Significantly different (P≤0.01) from the chamber control group by Dunnett's test (left cauda epididymis weights) or Shirley's test (sperm/mg cauda epididymis and sperm/cauda epididymis measurements). Data are presented as mean ± standard error. n=9

Genetic Toxicology

α-Pinene (5 to 10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98 or TA100 or in *Escherichia coli* strain WP2 *uvrA*/pKM101 with or without rat liver S9 activation enzymes

INTP, 2016). There were no increases in the frequencies of micronucleated erythrocytes in male or female mice treated in a 3-month study (NTP, 2016).

Turpentine oil was negative in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, both in the presence and absence of a metabolic activation system from rat liver, did not increase chromosomal aberrations in human lymphocytes in either the presence or absence of a metabolic activation system, and was negative in the TK+/− test in L5178Y mouse lymphoma cells (MAK, 2019). α-Pinene, both in the presence and absence of a rat liver metabolic activation system, was not mutagenic in the Salmonella typhimurium strains TA97a, TA98, TA100, TA1535, TA1537, and TA1538 (MAK 2017).

Two *in vitro* genotoxicity studies of α-pinene were performed using mammalian cells. α-Pinene did not induce DNA damage as assessed by the comet assay in human lung A549 cells in a system that allowed exposure to α-pinene by air (concentrations ranged from 1 to 1,800 mg/m3) (Gminski *et al*., 2010). However, α-pinene was clastogenic and aneugenic in V79-C13 Chinese hamster cells exposed in cell culture medium (Catanzaro *et al*., 2012). Clastogenic activity was evidenced by induction of DNA damage assessed by the comet assay, significant increases in micronucleated cells, and induction of chromosomal breakage assessed by metaphase analysis. With regard to the mechanism of DNA damage, α-pinene generated significant increases in reactive oxygen species as measured by a fluorescence assay. Furthermore, a significant number of the micronuclei observed in the V79-C13 cells stained positive for the presence of kinetochores. The authors concluded that a-pinene is able to compromise genome stability both directly through mitotic spindle alterations that lead to disordered chromosome segregation and indirectly through ROS production that induces DNA damage (Catanzaro, 2012).

Epidemiologic Studies

Epidemiologic studies of turpentine alone are not available. Turpentine has been evaluated in case-control studies of woodworkers and populations exposed to turpentine and others chemicals through occupational and personal exposure**.**

Table 6. Epidemiologic Studies

	Study Design	Findings	Discussion
1	A nested case-control design was applied in a cohort of Finnish male woodworkers. 7307 workers from 35 plants were followed up for the development of respiratory cancer. The cohort comprised workers in sawmill (n = 2531), plywood (n = 1775), furniture (n = 1483), construction carpentry factories (n = 876), particle board (n = 630), and workers producing glues for the wood industry (n = 12). A job exposure matrix was used to categorize exposure. Less data were available on phenol, pesticides, terpenes, engine	No indications of raised risk or exposure-response relation concerning exposure to wood dust were found. Three of the seven cases of adenocarcinoma (43%) were exposed to wood dust, which was fewer than among the rest of the cases of lung	Exposure to wood dust was not associated with respiratory cancers. The occurrence of one nasal cancer matched what was expected for the cohort. Exposures to terpenes and mold spores were slightly associated with respiratory cancers, which may be due to chance, although the role of

	Study Design	Findings	Discussion
	exhaust, chlorophenols, solvents, caseinalbumin glues, melamine glues, mold spores, and bis(chloromethyl)ether. For these, a qualitative (yes/ no) and a simple quantitative (the duration of exposure) indicator were used. Analyses were adjusted to control for vital status and smoking. The respiratory cancers were primary malignant neoplasms at sites with a possibility of direct epithelial contact with inhaled agents-namely, lungs, trachea (ICD-7code 1620-1; n = 117 cases); larynx, epiglottis (161; n = 12); tongue (141; n = 3); pharynx (145-8; n = 2); mouth, other (143-4; n = 1); and nose, sinuses (169; n = 1). In most statistical analyses, all respiratory cancers were pooled because the number of exposed cases was small for most exposures.	cancer (64%), or among all controls (60%). The subjects were mainly exposed to softwood dust. Exposure to terpenes and other heating products of pine and spruce were only weakly associated with respiratory cancers. Only exposure to phenol and diesel exhaust were associated with significantly elevated risk of respiratory cancer.	occupational exposure cannot be ruled out.
2	Cases were 538 children aged 19 years who were newly diagnosed with confirmed neuroblastoma in 1992–1994 and were registered at any of 139 participating hospitals in the United States and Canada. Self-reported exposures were reviewed by an industrial hygienist, and improbable exposures were reclassified. Effect estimates were calculated using unconditional logistic regression, adjusting for child's age and maternal demographic factors.	Maternal exposures to most chemicals were not associated with neuroblastoma. Paternal self-reported exposures to turpentine (OR = 1.9; 95% CI: 1.0 – 3.6) and IH-corrected exposures (OR = 10.4, 95% CI: 2.4 – 44.8) were associated with an increased incidence of neuroblastoma, as were exposures to wood dust (OR = 1.5; 95% CI: 0.8, 2.8). When data were adjusted for paternal exposures to common hydrocarbons and paints, odds ratios for turpentine (OR _ 12.0; 95 percent CI: 2.2, 65.9) remained elevated, whereas the odds ratio for paint thinner was diminished (OR = 0.9; 95 percent CI: 0.4, 2.1).	Tumor mechanism not evident. Mutations could occur during gametogenesis in the mother or father and would then be inherited by the child, or they could occur sporadically in target tissues of the developing fetus or child. Paternal occupation as a painter was associated with a twofold increase in the incidence of neuroblastoma in offspring. However, in analysis of specific chemical exposures, there is little evidence that exposure to paints accounts for this association. The increased risk in painters may instead result from the use of solvents such as mineral spirits, paint/lacquer thinner, or turpentine during the painting process.

	Study Design	Findings	Discussion
3	Population-based, incidence case-control study involving 376 Non-Hodgkins Lymphoma (NHL) cases and 463 population controls selected from the Medicare beneficiary files and S driver's license records. Cases were newly diagnosed with NHL during the three-year period between 1 October 1995 and 30 September 199. Exposure information was obtained by telephone interview which asked about exposure to "paint thinners/turpentine". Cumulative occupational exposure was calculated based on the number of hours exposed (per day, week, month or year), the years of first and last exposure, and the total number of years/months. Home use of paint products and cleaning solvents were answered as either the average frequency per year or cumulative times used during adult life time and the former was translated into the cumulative number of uses based on the frequency and duration of adult life period. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using an unconditional logistic regression model, adjusting for a number of risk factors for NHL	Work exposure to paint thinners/turpentine: Cases/controls: 17/8 OR (95% CI): 1.8 (0.67 – 4.94) Home exposure to paint thinners/turpentine: Cases/controls: 165/189 OR (95% CI): 1.43 (0.97 – 2.08) When work and home combined and analyzed together, the risk of NHL associated with any exposure, compared to no exposure at either job or home, was a statistically significantly increased (OR= 1.46, 95% CI: 1.05-2.03). This observation was more pronounced for B-cell lymphoma and for low-grade lymphoma with ORs of 1.52 (95 CI: 1.08-2.14) and 2.20 (95% CI; 1.42-3.41), respectively.	Authors found that occupational exposure to any solvent beginning prior to 1970 resulted in a statistically significant increase in risk of NHL (OR= 1.87, 95% CI 1.03-3.40). Study limitations: questionnaire limited to only paint-related products; potential recall bias due to case/control and selection bias due to low response rate.
4	Large-scale case-control study involving 1842 acute lymphocytic leukemia (ALL) cases and 1986 matched controls. The study examined the association of self-reported occupational exposure to various hydrocarbons among parents with risk of childhood ALL by exposure time window, immunophenotype of ALL, and age at diagnosis. Self-reported exposures were collected by telephone interview. Participants were asked during the interview about specific exposures, *i.e.,* solvents, degreaser or cleaning agents (*e.g.,* carbon tetrachloride, trichloroethylene, benzene, toluene, xylene, and others), plastic materials (*e.g.,* polyvinyl chloride,	For turpentine: Maternal (Cases/Controls) Anytime (23/20): 1.4 (0.8–2.6) Pre-conception (16/9): 1.9 (0.8–4.5); During pregnancy (15/5): **3.5 (1.3–10.0);** Post-natal (16/12): 1.6 (0.8–3.5) Paternal (Cases/Controls)	Authors concluded that study suggested that parental, mainly maternal, occupational exposure to hydrocarbons was associated with an increased risk of childhood ALL. Study limitations: recall bias, no exposure intensity.

	Study Design	Findings	Discussion
	polystyrene, polyethylene, polyurethane, and others), paints, pigments or thinners (spray paints, printing inks, lacquers, turpentine, and others), and oil or coal products (*e.g.,* coal, cooling and cutting oils, and others). Exposures to both individual chemicals and to grouped chemicals were analyzed by exposure windows, as well as by age at diagnosis and immunophenotype of ALL.	Anytime: 145/103 1.1 (0.8–1.5) Pre-conception: 109/81 1.1 (0.8–1.5) During pregnancy: 59/27 **1.7 (1.1–2.8**) Post-natal 75/38 **1.5 (1.0–2.2)**	

1. Hedenstierna, 1983. 2. De Roos 2001. 3. Kato 2005. 4. Shu 1999.

Recommendation

An 8-hour PEL for turpentine (CAS number 8006642) and selected monoterpenes (alpha-pinene, beta-pinene, and delta-carene, CAS numbers 80568, 127913, 13466789 respectively) of 20 PPM is proposed for discussion. The extrapolation to an 8-hour effect from the 2-hour human exposure studies seems reasonable as an RD50 extrapolation supports a PEL of 34 ppm. Workplace studies with approximately 10 ppm and low dust levels suggests turpentine is a contributing factor to irritation under these conditions.

The human volunteer studies with turpentine, pinene, and carene indicate significant irritation after exposure to 80 ppm for 2 hours with light physical activity. Mostly non-significant effects of upper respiratory tract inflammation were seen with these effects, tracking the irritancy potency of the monoterpenes: carene > pinene > turpentine. Using a simple concentration x time relationship, exposure at 20 ppm for 8 hours would be equivalent to exposure at 80 ppm for 2 hours. The studies by Erikkson supports this extrapolation in that significant eye irritation was observed after an 8-hour work shift during which sawmill workers were exposed to 6.5 – 15.3 ppm (GM) and saw dust levels ranging from 0.2 to 0.4 mg/m^3 though the effect of dust exposure may have been a contributing factor. More robust volunteer exposures (Johard, four 3-hr 80 ppm exposures over two weeks; Erikkson, 8-hour exposure to approximately 10 ppm terpenes and saw dust) have detected inflammation markers that indicate these effects could occur at 20 ppm, though the effects of saw dust in these studies cannot be discounted. Lung function has mostly been unaffected in these studies, with reduction in carbon monoxide diffusion capacity being the only significant respiratory effect.

Animal studies with turpentine or select monoterpenes are limited and do not provide a good basis for hazard assessment. The NTP 3-month study with alpha-pinene identified several effects – liver weight increases in both species, male rat kidney lesions – that are considered either an adaptive response to treatment (enzyme induction) or not relevant to human (male rat tumors are expected to be a result of the alpha-2-globulin mechanism). Another basis for hazard assessment would be the occurrence of transitional hyperplasia in mouse bladder (Table 4). The primary effect in mice caused by exposure to α-pinene was an increased incidence of transitional epithelium hyperplasia of the urinary bladder in males and females exposed to 100 ppm or more, the severity of which

increased with increasing exposure concentration. NTP stated that this finding is uncommon in subchronic studies but also that hyperplasia is often noted in studies of urinary bladder carcinogens in mice (2016). NTP further noted that there are two types of hyperplasia in the urinary bladder:

> "Reparative hyperplasia is a common secondary response to inflammation and/or necrosis in the urinary bladder and may also occur when urinary calculi (solid particles or "stones") are present. Preneoplastic hyperplasia of the transitional epithelium is considered a component lesion in the continuum to neoplasia in the urinary bladder, and when present, cellular atypia or atypical growth patterns may provide plausible evidence that the hyperplasia is preneoplastic"

Specific histopathologic indicators of either type of hyperplasia (e.g., calculi for reparative, cellular atypia for preneoplastic) were not evident in male or female mice from the NTP study. The rapid onset of hyperplasia in both male and female mice (60-70% incidence at 100 ppm, 100% at higher doses, see table below) suggests a threshold process that has resulted in calculi formation at 100 ppm and above. Using 50 ppm as the NOAEL for bladder hyperplasia, MAK established an OEL of 5 ppm, using an uncertainty factor for a possible increase in the effects over time (1:2), the extrapolation from animals to humans (1:2) and the increase in respiratory activity of humans at the workplace (1:2) (MAK, 2017).

The reproductive effects observed in rats and mice in the NTP study also provide a basis for turpentine hazard assessment. The number of sperm per cauda epididymis was significantly reduced in both male rats and mice exposed to 200 and 400 ppm alpha-pinene. Using 100 ppm as a NOAEL for this effect and applying an uncertainty factor of 1000 (10 for subchronic to chronic, 10 for intraspecies variability, and 10 for interspecies variability) results in human equivalent concentration of 0.1 ppm. Adjusting this value for the percent of pinene in turpentine (60%) and scaling the animal exposure to worker exposure (6 hour/ 8 hour) results in an OEL of 0.2 ppm. NTP noted that there was an accompanying minor decrease in epididymal weights that did not reach significance and that raises the possibility that the change in absolute sperm per cauda was due to a decrease in epididymal weight cannot be ruled out. Other sperm parameters measured in these studies (spermatid heads and sperm motility) were not affected by treatment. The significance of this effect on caudal sperm count in this study to human hazard assessment is not clear. NTP (2016) concluded that further studies on the effects of α-pinene on reproductive function are warranted.

The effect of turpentine in the cited epidemiologic studies is either weak or confounded due to co-exposure to other chemicals. All of the studies are case-control and relied on subject/proxy recall of exposure and therefor are potentially subject to recall bias and exposure misclassification. No study has a quantitative measure of exposure concentration so applying these findings to hazard assessment is problematic.

Usage information:

Table 6. CERS Usage Data by California Industries

SIC Group	Industry	# Users* (gal/lbs)	Average Daily Amount
14	Mining & Quarrying of Nonmetallic Minerals	1	30 gal
25	Furniture & Fixtures Manufacturing	1	3 gal
27	Printing, Publishing and Allied Industries	1	0 gal
28	Chemicals and Allied Products Manufacturing	9 (5/4)	457/203 gal/lbs
29	Petroleum Refining & Related Industries	1	500 gal
34-38	Machinery & Equipment Manufacturing	10 (9/1)	65/1 gal
42-47	Transportation & Warehousing	7	505 gal
49	Sanitary Services	3	19 gal
50-51	Wholesale	8	12/1077 gal/lbs
52-53	Retail	5	1.2 gal
65	Real Estate	2	5.5 gal
70-79	Business Services	6 (5/1)	0.44/0.23 gal/lbs
80	Health Services	3	1.04 gal
82	Educational Services	27(26/1)	2.2/0.5 gal/lbs
866	Religious Organization	1	0 Gal
873	Research, Development & Testing Services	6	0.22 Gal
91-95	Public Administration	4	3.25 Gal
	Unidentified Industry (warehouse)	1	1723 Gal
		Total Users: 96	

*Number of entries in CERS reporting turpentine use in gallons or pounds.

Measurement Information

NIOSH Method 1551 (fully validated) uses a coconut shell charcoal tube at a flow rate of 0.01 to 0.2 L/min with a sample volume of 1 to 10 L. The sample is analyzed with GC-FID. The estimated detection limit is 0.1 mg per sample and the working range is 9 to 360 ppm for a 10-L air sample.

For terpenes NIOSH Method 1552 (partially validated) uses a coconut shell charcoal tube at a flow rate of 0.01 to 0.2 L/min with a sample volume of 2 to 30 L. The sample is analyzed with GC-FID. The estimated detection limits for α-pinene, β-pinene and 3-carene are 0.6, 0.4 and 0.3 ug per sample respectively. The working range is 0.02 to 36 ppm for a 15-L air sample.

Based on this information, there are no anticipated concerns with analytical feasibility.

Recommended Workplace Controls and Feasibility Issues

The Division is seeking stakeholder input on these subjects.

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APPENDIX: HUMAN EXPOSURE STUDIES WITH TERPENES

PINENE

Table 3. Preexposure lung function values and the percentage of change 30 min after a 2-h inhalation exposure (50 W) to (+)-α-pinene at concentrations of 10 and 450 mg/m³. ($FEV_{1.0}$ = forced expiratory volume in 1 s, VC = vital capacity, RV = residual volume, PEF = peak expiratory flow, MEF_{50} = mean expiratory flow at 50 % of the VC, sGaw = conductance, Raw = resistance)

	$FEV_{1.0}$ (l)		VC (l)		RV (l)		PEF (l)		MEF_{50} (l/s⁻¹)		sGaw (l/kPa/s)		Raw (kPaxs/l)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Preexposure value	4.8	0.6	6.6	0.7	2.9	1.1	12.7	2.8	5.2	1.1	2.1	1.0	0.14	0.05
Percentage of change after 30 min														
10 mg/m³	0.5	0.1	−0.1	13	−5.8	24	0.4	13	1.7	5.6	16	55	−25	23
450 mg/m³	3.4	4.7	0.8	6.4	1.5	26	3.2	12	5.5	7.6	5.4	49	−25	26

CARENE

THE MEAN VALUES AND STANDARD DEVIATION OF LUNG FUNCTION VALUES AT PREEXPOSURE AND ABOUT 30 min AFTER A 2-hr INHALATION EXPOSURE (50 W) TO 3-CARENE AT CONCENTRATIONS OF 10 (CONTROL) AND 450 mg/m³ (HIGH) AND THE MEAN INDIVIDUAL DIFFERENCE AFTER HIGH AND LOW EXPOSURE IN PERCENTAGE

	Preexposure	10 mg/m³	450 mg/m³	diff (450–10) (% of control)
VC_{max} (liter)	6.3 (1.0)	6.2 (1.1)	6.3 (1.1)	−0.60 (2.59)
FVC (liter)	6.3 (1.0)	6.2 (1.2)	6.3 (1.1)	−0.07 (2.85)
$FEV_{1.0}$ (liter)	5.1 (0.6)	5.1 (0.6)	5.2 (0.6)	0.67 (2.70)
RV (liter)	2.1 (0.6)	2.6 (0.5)	2.5 (0.6)	0.72 (9.14)
TLC (liter)	8.4 (1.3)	8.7 (1.3)	8.6 (1.2)	−0.20 (2.86)
MEF_{50} (liter/s)	6.0 (1.5)	5.9 (0.9)	6.1 (1.1)	1.7 (5.0)
PEF (liter/s)	12.4 (2.0)	12.1 (1.1)	12.2 (2.0)	−3.0 (5.2)
sGaw (liter/(kPa · s))	1.9 (0.6)	2.0 (0.4)	1.9 (0.5)	−7.8 (23.0)
Raw (kPa · s/liter)	0.12 (0.04)	0.11 (0.02)	0.12 (0.04)	17.1 (34.2)

Note. $FEV_{1.0}$, forced expiratory volume in 1 second; VC, vital capacity; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity; MEF50, mean expiratory flow at 50% VC; Raw, airways resistance; and sGaw, specific conductance.

TURPENTINE

Table 3 Mean (SD) lung function variables before exposure and about 30 minutes after two hours inhalation exposure to terpentine at a concentration of 450 mg/m³, during physical exercise at a workload of 50 W (values are of six subjects (seven for 3-carene exposure))

	Turpentine		*Effect of exposure (change as % of before exposure value)*		
	Before exposure	*After exposure*	*Turpentine (450 mg/m³)*	*3-Carene (450 mg/m³)*[10]	*3-Carene (450 mg/m³)*[10]
VC_{max} (l)	6·3 (1·0)	6·1 (1·1)	−1·8 (2·2)	−0·34 (2·1)	0·08 (1·8)
FVC (l)	6·3 (1·0)	6·2 (1·1)	−1·4 (2·7)	−1·1 (2·0)	−1·1 (2·6)
FEV_1 (l)	5·1 (0·6)	5·1 (0·5)	1·7 (4·2)	2·4 (3·2)	2·5 (2·1)
RV (l)	2·1 (0·6)	2·5 (0·5)	28 (32)	20 (21)	26 (19)
TLC (l)	8·4 (1·3)	8·5 (1·7)	3·5 (5·6)	3·3 (5·1)	4·7 (3·6)
MEF_{50} (l/s)	6·0 (1·5)	6·0 (1·0)	3·0 (7·8)	3·1 (9·9)	4·9 (6·6)
PEF (l/s)	12·4 (2·0)	12·0 (1·0)	−3·8 (8·1)	−1·4 (6·9)	1·7 (10)
sGaw (l/kPa.s)	1·9 (0·6)	1·5 (0·3)	17 (74)	36 (100)	57 (120)
Raw (kPA.s/l)	0·12 (0·04)	0·15 (0·03)	29 (32)	−5·7 (45)*	−21 (38)*

*P < 0·05 Student's *t* test, turpentine *v* 3-carene exposure.
FEV_1 = forced expiratory volume in 1 second; VC = vital capacity; PEF = peak expiratory flow; RV = residual volume; TLC = total lung capacity; MEF_{50} = mean expiratory flow at 50% VC; Raw = airway resistance; sGaw = conductance.

TURPENTINE – EXTENDED EXPOSURE Johard 1993

TABLE I. General Characteristics of the BAL Fluid Recruited From 8 Nonsmoking Healthy Volunteers Before and After Exposure to Terpenes*

				Differential cell count				
Status	Recovery (%)	Viability (%)	Cell conc ($\times 10^6$/L)	Ma ($\times 10^6$/L)	Ly ($\times 10^6$/L)	PMN ($\times 10^6$/L)	Eos ($\times 10^6$/L)	Mast /10 vf
Before exposure	68 (66–76)	90 (87–93)	76 (61–125)	72 (58–114)	2 (2–7)	2 (1–3)	0 (0–0)	1 (0–2)
After exposure	66 (60–74)	93 (91–96)	126[a] (122–166)	121[a] (111–156)	3 (2–6)	3 (2–4)	0 (0–2)	5[a] (3–6)

*Data are given as medians with interquartile ranges. Ma = macrophages; Ly = lymphocytes; PMN = polymorphonuclear neutrophils; Eos = eosinophils; Mast = mast cells/10 visual fields (vf) with a magnification of 16 times.
[a]$p < 0.05$ when data were compared before and after exposure.

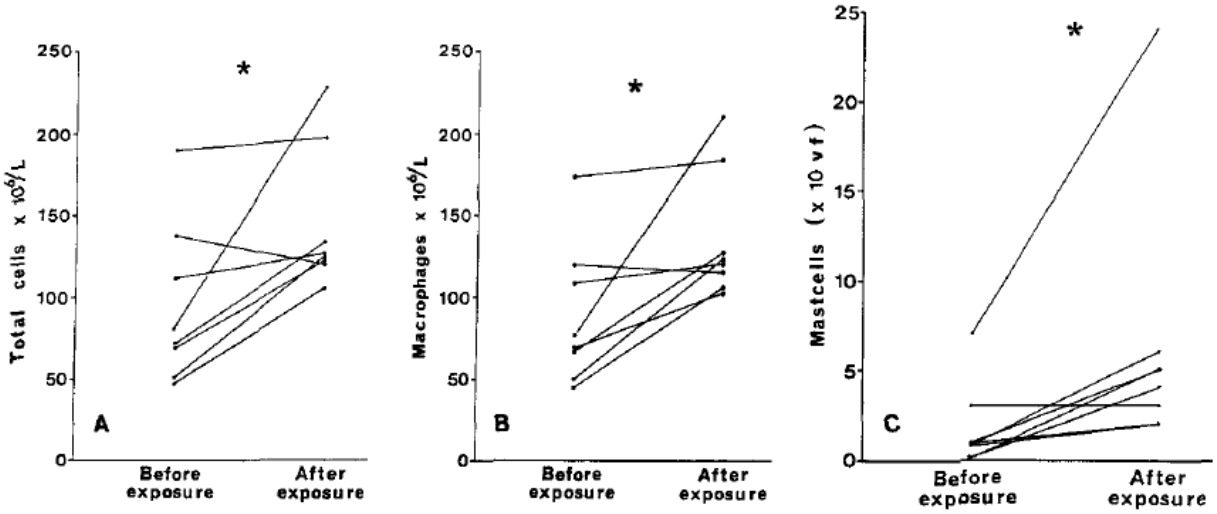

Fig. 1. Total cell concentration, macrophage concentration, and number of mast cells in BAL fluid before and after terpene exposure in 8 healthy subjects. * = $p < 0.05$. **A.** Total cell concentration. **B.** Macrophage concentration. **C.** Number of mast cells/10 visual fields (magnification $\times 16$).

TABLE II. Soluble Substances of the BAL Fluid Recruited From 8 Nonsmoking Healthy Volunteers Before and After Exposure to Terpenes*

Status	Albumin mg/L	Fibronectin µg/L	Native fibronectin µg/L	Hyaluronan µg/L	Tryptase mU/L
Before exposure	41 (37–50)	54 (33–130)	51 (30–117)	6 (6–8)	62 (48–119)
After exposure	35 (34–38)	48 (37–81)	40 (26–77)	8 (6–9)	117 (62–145)

*Data are given as medians with interquartile ranges. No statistically significant differences were observed.