J. Toxicol. Pub. Health
Vol. 16, No. 4, pp. 303-309, 2000

Subchronic Inhalation Toxicity of iso-Butylalcohol in Rats

Beom-Su Jang[1], Jong-Hwan Lim[1], Hyo-In Yun[1], Jong-Il Park[2], Chang-Su Ha[2], Jong-Choon Kim[2], Hyeon-Yeong Kim[3], Yong-Hyun Chung[3], Jae-Hwang Jeong[3] and Yong-Muk Lee[3]

[1]*College of Veterinary Medicine, Chungnam National University, Daejon, Korea*
[2]*Toxicology Research Center, Korea Research Institute of Chemical Technology, Daejon, Korea*
[3]*Center for Occupational Toxicology, Occupational Safety and Health Research Institute, Daejon, Korea*
(Received August 21, 2000)
(Accepted November 27, 2000)

ABSTRACT *: The purpose of this study is to investigate toxic effects of iso-butylalcohol (iBA) in Sprague-Dawley (SD) rats under the exposure of 6 hours a day, 5 days a week for 13 weeks by inhalation, and to evaluate the occupational safety of iBA in comparison with the permissible exposure level (PEL) stipulated by the Occupational Safety and Health Administration (OSHA). iBA did not induce any abnormal changes from the aspects of clinical signs, feed consumption, ophthalmic test, urinalysis, hematology and blood chemistry during and at the terminal of the inhalation toxicity tests. We did not find any abnormal findings in the gross and microscopic observations due to the inhalation of iBA. There was no alteration in relative organ weights by the inhalation of iBA. No observed adverse effect level (NOAEL) of iBA was considered to be more than 3,000 ppm in rats under the inhalation of 6 hours a day, 5 days a week for 13 weeks. Fifty ppm of iBA, the PEL regulated by OSHA, is too conservative for working places. As iBA showed no abnormal observations in all the experimental parameters at any concentration under this experimental condition, we suggest that 150 ppm is safe enough for the PEL of iBA in the working areas, even taking into consideration that OSHA lowered the PEL to 50 ppm for fear of the probable risk of its skin irritation.*

Key Words *: iso-Butylalcohol, Inhalation Toxicity, PEL, NOAEL*

I. INTRODUCTION

The safety of cleaning solvents for industrial use is very important because many workers are exposed to the large amount of solvents every day during the working hours. Halons have been used as cleaning solvents, which are being replaced by other alternatives because of their ozone-depleting and global warming characteristics (EPA, 1996). In Korea, 2-bromopropane (2-BP) has been used in place of halons. However, 2-BP was found to cause reproductive and hematopoietic disorders in the local workers exposed to 2-BP-containing solvents (Takeuchi *et al.*, 1997; Kim *et al.*,1996, Park *et al.*, 1997; Appleman *et al.*, 1982; Bilzer *et al.*, 1990), which made the Korean Ministry of Labor establish the threshold limit value (TLV) of 2-BP in the work place as 1 ppm (Gibel *et al.*,1974).

Owing to the toxicity of 2-BP, there have been many concerns about toxicity of other cleaning solvents, especially with the large consumption volume in industrial sectors. Iso-butylalcohol (iBA) is ranked as the 288th among all circulated chemicals in Korea. iBA is inflammable and colourless liquid with a sweet odor similar to that of amyl alcohol. It has a boiling point of 108, a water solubility of 8.7%, with the n-octanol/water partition coefficient of 0.83. Its vapour is 2.6 times denser than air. It occurs not only naturally as a product of fermentation but also is synthesized from petrochemicals. It is used as an organic solvent, a plasticizer and a flavouring agent. It is consumed for the manufacture of isobutyl esters and perfumes. iBA is readily biodegradable and does not bioaccumulate. In animals, iBA is absorbed through the skin, lungs, and gastrointestinal tract. It is metabolized by dehydrogenases to isobutyric acid via aldehyde intermediate and may enter the tricarboxylic acid cycle. Small amounts of iBA are excreted unchanged (<0.5% of the dose), and as a glucuronide form (<5% of the dose) in the urine. In rabbits,

*To whom correspondence should be addressed

metabolites found in the urine include acetaldehyde, acetic acid, isobutylaldehyde, and isovaleric acid. TLV for iBA in working air is recommended as 50 ppm by American Conference of Governmental Industrial Hygienists (ACGIH). Occupational Safety and Health Administration (OSHA) stipulated that the permissible exposure level (PEL) of iBA be 50 ppm. Gibel *et al.(1974)* reported that iBA had tumorigenic effects on the skin, gasrtointestinal track and liver during 71-week oral and 73-week subcutaneous administration experiments. But those toxicities of iBA were not confirmed by other investigators and there are very few data available on the inhalation toxicity of iBA and its established PEL in working places.

This study was carried out to assess the 13-week subchronic inhalation toxicity of iBA and to evaluate the PEL of iBA (50 ppm) in working places.

II. MATERIALS AND METHODS

1. Chemicals

Chemicals used in this study were of the reagent grade and purchased from commercial sources. Isobutylalcohol (Test No. dj80218M) was obtained from Daejung Chemical & Metals Co., Ltd. (Seoul, Korea).

2. Animals

Five-week-old Sprague-Dawley (SD) rats (SPF grade) of both sexes were purchased from Daehan Laboratory Animal Research Center Co., Ltd. (Eumseong, Korea), After one week of acclimation, 40 males (171.23±4.83 g) and 40 females (139.23±5.06 g) were used for subchronic inhalation toxicity test. Rats were housed individually in wire-bottomed 5-straight stainless-steel cages placed in exposure chambers. The chambers were maintained at 23±2°C, 40~70% humidity, 12 h light/12 h dark cycle (light during 09:00~21:00), 11~15 times ventilation/h, and 5~15 mmAq negative pressure. Rats were fed with the sterilized pellet (Jeil Feed Co., Ltd., Taejon, Korea) and the sterilized tap water *ad libitum* through both the acclimation and observation periods.

3. Condition of chambers

Temperature, relative humidity, pressure and air ventilation were recorded by the environmental controller (Model No. ICS-20RG, Shibata Co., Ltd., Japan). Calibration of the concentration of iBA in chambers was carried out using the standard (Lot No. 7B2212, Junsei Chem. Co., Ltd., Japan), air pump (Model APN-110KV-1, Iwaki Co., Ltd., Japan), gas meter (Model DC-2A, Shinagawa Co., Ltd., Japan), and Teflon bags. Detection condition of gas chromatography (GC) (Model GCS-14PFFS, Shimadzu, Japan) for iBA was as follows: detector, FID; column, silicon DC-200 15% Chromosorb with mesh of 80/100 and 0.5 m length; detector temperature, 150°C; oven temperature, 100°C; injector temperature, 150°C; injection volume, 1 m*l* of gas sample. The concentration of iBA in chambers during the exposure was recorded by the GC every 15 minutes.

4. Environmental monitoring in chambers

Temperature, relative humidity, pressure, air ventilation and illumination cycle in the inhalation chambers were measured under the OECD guidelines for environmental control. All rats were housed at the temperature of 23.63±0.94°C, the relative humidity of 59.15±0.87%, the pressure of -10.09±0.20 mmAq, the air ventilation of 207.77±2.62 *l*/min (12/h) (Table 1). These parameters and the concentrations of iBA in each chamber were within the established value±2%.

Table 1. Environmental condition and concentration of iso-butylalcohol in the inhalation chamber during the experiment

Items	Group 0 (Control)	Group 1 (333 ppm)	Group 2 (1,000 ppm)	Group 3 (3,000 ppm)
Iba Concentration (ppm)	0	333.1±1.99	1008.51±1.36	3005.7±36.12
T (°C)	23.8±2.62	23.3±0.88	23.5±0.93	23.9±0.98
RH (%)	62.9±7.86	58.9±8.72	58.1±8.75	56.8±8.35
P (mmH_2O)	-10.0±0.15	-10.0±0.13	-10.2±0.24	-10.1±0.23
R (*l*/min)	207.8±2.62	207.1±2.01	207.6±2.20	208.6±3.27

T, Temperature; RH, Relative Humidity; P, Pressure; R, Flow rate
All data values are expressed as total mean±SD from the 13-week data.

5. Animal experimentation

Whole-body exposure chambers (Model No. SIS-20RG, Shibata Co., Ltd., Japan) including gas generator (Model No. VG-4R, Shibata Co., Ltd., Japan) were used for exposure of iBA to animals. For a subchronic inhalation experiment, groups of 10 male and female rats were exposed to 0 (control), 333, 1,000 and 3,000 ppm for six hours a day, five days a week, for thirteen weeks. This experimental design was based on the usual working schedule of workers. By reference to the PEL of iBA, we used 20 times PEL as a middle concentration (1,000 ppm), with a third (333 ppm) and three times (3,000 ppm) of this concentration. All animals were inspected daily for the clinical signs. Body weights and food consumption were measured once a week during the inhalation period. Urine samples were collected 24 hours before the completion of the experiment, and analyzed for red blood cells, white blood cells, bilirubin, urobilinogen, ketones, protein, nitrite, glucose, pH, specific gravity using a test strip (Cambur-9, Boehringer Mannheim, Germany). All animals were anesthetized with diethylether, and bled for hematology and biochemistry from the posterior vena cava. In hematological examinations, white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell volume distribution width, platelet count, differential leucocyte count and mean platelet volume were determined by a hematological auto-analyzer (Sereno Co, Ltd.,U.S.A.). In serum biochemical examinations, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, blood urea nitrogen, protein, cholesterol, creatinine, sodium and total bilirubin were determined by a biochemical analyzer 50 Express (Ciba Corning Co., U.S.A.). Organ weights were measured for the thymus, adrenal, testis, heart, lung, kidney, spleen, liver and brain. These tissues were taken and fixed in 10% neutral buffered formalin. The tissues were processed for standard paraffin embedding prior to sectioning at 5 μm and stained with hematoxylin-eosin and/or PAS-hematoxylin.

6. Statistical analysis

Data were expressed as means±SD. Statistical analyses were performed by one-way analysis of variance (ANOVA) and the comparisons between groups were tested using Duncan's *t*-test. Differences were considered to be significant at $p<0.05$.

III. RESULTS

1. Clinical findings

All treated groups were not observed to show decreased activity and any abnormal behaviour or posture.

2. Body weights

Changes in body weight during the whole inhalation period are shown in Fig. 1 (for males) and Fig. 2 (for females). There were no statistically significant differences in the body weight in male or female rats during the 13 weeks experiment due to the inhalation of iBA.

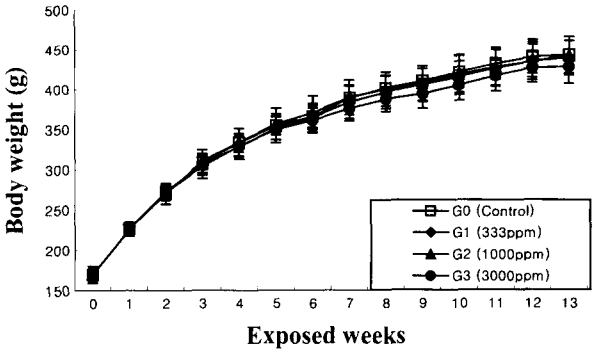

Fig. 1. Body weight changes in male rats during a 13-week period of the iso-butylalcohol inhalation.

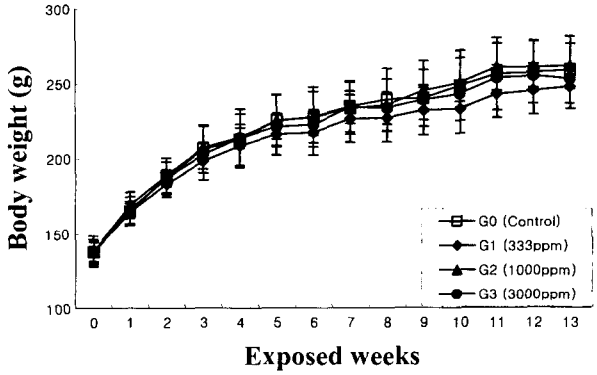

Fig. 2. Body weight changes in female rats during a 13-week period of the iso-butylalcohol inhalation.

3. Food consumption

There were no statistically significant changes in food consumption between the control group and the treated groups (Table 2).

4. Urinalysis

Glucose, urobilinogen and bililubin in the urine of the control and all treated groups were shown normal or negative (data not shown).

Table 2. Food consumption in male and female rats after inhalation of iso-butylalcohol during the experiment

(Unit : g/day/rat)

Sex	Group 0 (Control)	Group 1 (333 ppm)	Group 2 (1,000 ppm)	Group 3 (3,000 ppm)
Male	22.1±1.85	21.7±1.87	21.9±2.05	21.7±2.20
Female	15.4±1.65	14.9±1.87	15.4±1.76	14.9±1.68

5. Necropsy findings

There were no gross pathological findings in all the animals.

6. Relative organ weights

The relative organ weights (mg organ weight/100 g body weight) are summarized in Table 3 for the males and the females. There were no statistically significant changes in the relative organ weights between the control group and the treated groups.

7. Hematology

Table 4 shows that hematocrit, and mean corpuscular volume were increased and platelet decreased in the male of 333 and 3,000 ppm groups as compared to the control ($p<0.05$), but no difference was

Table 3. Relative organ weight of male and female rats exposed to iso-butylalcohol by inhalation for 13 weeks

(Unit : mg/100 g B.W)

Sex	Organ	Group 0 (Control)	Group 1 (333 ppm)	Group 2 (1,000 ppm)	Group 3 (3,000 ppm)
Male	Thymus	85.73±13.96	90.01±13.15	83.32±12.15	99.94±22.78
	Adrenal L	6.47±0.61	7.01±1.48	6.70±0.88	6.81±1.19
	Adrenal R	6.56±0.77	6.60±1.02	7.01±0.93	6.88±1.60
	Testis L	415.54±35.21	414.61±64.42	436.07±29.43	436.47±14.94
	Testis R	416.13±32.62	415.95±67.76	427.24±25.82	434.28±20.30
	Heart	307.27±22.52	320.58±17.31	310.29±17.57	306.43±15.68
	Thyroid L	2.48±0.54	3.69±1.86	3.27±1.21	2.96±0.71
	Thyroid R	2.65±0.96	3.62±1.90	3.45±1.11	2.82±0.60
	Kidney L	323.21±26.66	325.34±23.96	321.95±20.88	323.62±15.99
	Kidney R	315.11±24.63	323.54±29.25	320.48±26.19	329.49±19.51
	Spleen	170.15±49.89	175.05±21.25	171.37±16.64	176.10±15.89
	Liver	2591.95±149.53	2556.50±108.90	2574.07±97.86	2554.00±135.18
	Lung	425.43±24.75	450.86±103.31	438.15±34.10	434.12±32.24
	Brain	433.07±23.34	438.33±24.97	436.83±16.84	445.19±15.14
	Hypophysis	3.01±1.25	3.96±1.44	3.62±1.01	2.95±1.05
Female	Thymus	111.91±47.57	102.48±12.16	94.84±12.52	115.37±20.38
	Adrenal L	13.63±1.87	14.46±3.22	14.52±2.46	14.67±2.99
	Adrenal R	12.53±3.50	14.60±3.61	14.25±2.99	14.27±1.82
	Ovary L	17.71±3.59	19.60±4.30	20.80±4.35	22.96±5.50
	Ovary R	17.30±4.14	18.53±6.86	18.75±2.80	20.63±5.44
	Heart	346.24±25.92	342.95±12.93	350.79±23.78	364.80±74.52
	Thyroid L	2.89±1.09	3.79±0.78	3.47±0.99	3.71±0.84
	Thyroid R	3.54±0.86	3.85±1.62	3.10±0.63	4.09±0.84
	Kidney L	318.73±11.71	321.40±20.98	323.58±30.02	311.63±17.62
	Kidney R	322.14±18.85	332.17±19.78	320.66±21.88	323.42±28.14
	Spleen	221.35±31.42	216.18±7.70	217.35±13.65	222.58±29.50
	Liver	2509.95±145.39	2491.03±170.16	2451.97±112.07	2496.60±82.82
	Lung	526.83±39.38	541.59±39.60	558.80±24.08	534.14±35.50
	Brain	700.98±66.98	709.13±53.14	703.92±92.49	678.48±33.79
	Hypophysis	5.12±1.54	4.93±2.30	5.38±1.30	6.45±0.84

L: left; R: right
All values are expressed as mean±SD.

Table 4. Hematological results in male and female rats after inhalation of iso-butylalcohol for 13 weeks

Sex	Items	Group 0 (Control)	Group 1 (333 ppm)	Group 2 (1,000 ppm)	Group 3 (3,000 ppm)
Male	WBC	9.2±1.4	8.5±1.5	8.7±0.8	8.4±1.5
	RBC	6.9±0.2	7.0±0.2	6.8±0.2	7.0±0.2
	HGB	15.8±0.5	16.1±0.4	15.7±0.3	16.1±0.3
	HCT	36.7±1.3	38.8±0.9*	36.2±1.0	38.8±1.2*
	MCV	52.8±1.2	55.6±1.5*	53.4±1.5	54.9±1.1*
	PLT	0.9±0.1	0.7±0.1*	0.8±0.1	0.7±0.1*
	MPV	20.8±0.8	19.9±0.3*	20.5±0.8	18.3±5.0
	LYM	92.6±2.4	87.6±1.7	88.3±6.0	90.9±2.5
	GRAN	3.5±1.4	6.2±0.8	5.5±3.1	4.6±1.5
	MID	3.9±1.1	6.2±0.9	6.3±3.0	4.5±1.1
Female	WBC	4.4±1.0	4.9±1.4	5.6±0.7	6.3±1.2
	RBC	6.1±0.4	6.3±0.3	6.3±0.4	6.7±0.6*
	HGB	15.1±0.9	15.4±1.0	15.6±0.7	16.3±0.6
	HCT	33.5±2.9	34.5±2.5	35.6±2.7	38.0±1.2*
	MCV	54.7±1.5	55.1±1.8	56.3±1.4	56.9±1.6
	PLT	0.7±0.1	0.7±0.1	0.7±0.1	0.7±0.1
	MPV	20.9±1.7	20.6±1.8	20.8±2.1	19.1±0.6
	LYM	84.2±5.6	83.0±7.0	85.0±3.8	86.4±2.3
	GRAN	8.2±3.3	9.4±4.0	7.7±2.3	7.0±1.1
	MID	7.6±2.4	7.7±3.0	7.3±1.7	6.6±1.4

All values are expressed as mean±SD.
*Significantly different as compared with control by Duncan's *t*-test after ANOVA test($0.01<p<0.05$).
WBC, white blood cell count ($10^3/mm^3$); RBC, red blood cell count ($10^6/mm^3$); HGB, hemoglobin (g/dl); HCT, hematocrit (%); MCV, mean corpuscular volume (fl); PLT, platelet ($103/mm^3$); MPV, mean platelet volume (fl); LYM, lymphocyte in leucocyte (%); MID, mid-range population.

Table 5. Serum biochemical values in male and female rats after inhalation of iso-butylalcohol for 13 weeks

Sex	Items	Group 0 (Control)	Group 1 (333 ppm)	Group 2 (1,000 ppm)	Group 3 (3,000 ppm)
Male	TP	9.6±0.3	9.9±0.2*	10.1±0.3*	10.0±0.2*
	BUN	10.9±1.4	10.4±0.7	11.2±1.5	11.4±1.5
	TG	32.1±6.8	30.0±10.4	27.9±13.1	37.2±14.6
	ALB	4.4±0.2	4.5±0.2	4.7±0.1*	4.6±0.2*
	GLU	268.7±79.0	247.1±46.0	240.1±52.8	265.0±26.3
	AST	93.7±12.1	84.6±8.9	89.7±24.7	90.2±16.0
	ALT	36.8±4.8	31.3±6.5	35.1±6.5	37.4±6.9
	LDH	704.4±278.7	696.7±161.7	589.4±255.9	578.1±219.5
	ALP	92.7±16.0	95.6±10.8	100.1±14.3	105.4±13.9
Female	TP	9.7±0.5	9.7±0.3	9.8±0.3	9.9±0.3
	BUN	14.1±2.0	14.0±1.4	14.6±0.8	13.5±1.6
	TG	21.6±10.8	23.0±8.8	37.8±38.1	24.7±10.4
	ALB	4.2±0.5	4.3±0.3	4.3±0.2	4.4±0.3
	GLU	117.2±29.1	97.1±30.0	105.9±28.6	109.7±42.6
	AST	114.1±22.3	108.2±31.1	98.4±38.4	115.7±29.6
	ALT	38.0±9.6	36.2±4.3	47.1±34.1	32.3±9.8
	LDH	1225.0±319.5	1117.2±435.1	1205.1±533.8	1068.2±209.5
	ALP	86.4±12.2	95.8±16.2	93.8±28.5	94.8±18.6

All values are expressed as mean±SD.
*Significantly different as compared with control by Duncan's *t*-test after ANOVA test($0.01<p<0.05$).
TP, total protein (g/dl); BUN, urea nitrogen in blood (mg/dl); TG, triglyceride (mg/dl); ALB, albumin (g/dl); GLU, glucose (mg/dl); AST, aspartate aminotransferase (IU/l); ALT, alanine aminotransferase (IU/l); LDH, lactate dehydrogenase (IU/l); ALP, alkaline phosphatase (IU/l).

shown in the male of 1,000 ppm group. In the female of 3,000 ppm group, red blood cell numbers and hematocrit were significantly higher than the control values ($p<0.05$) but other parameters were not signif-

icantly different.

8. Blood biochemistry

Table 5 shows the biochemical serum values in male and female rats after inhalation of iBA for 13 weeks. The levels of total protein of the male in 333, 1,000, 3,000 ppm treated groups were significantly higher than the control ($p<0.05$). Albumin in the male of the 1,000 and 3,000 ppm treated groups were significantly higher than the control group ($p<0.05$) but other parameters were not significantly different. All paramerters of female groups were not significantly different.

9. Histopathological findings

Protein cast or accumulation of some metal in the kidney, and granulomatous inflammation of lung were shown in some animals but with no dose-dependency.

IV. DISCUSSIONS

In working places of many manufacturies, cleaning solvents are used in large amount for various purposes. Much used halons for these purposes are being replaced due to their notorious environment-destroying effects. In Korea, 2-bromopropane was tried as an alternative but found to have reproductive and hematopoietic toxicities in rats and later in humans. Isobutylalcohol could be another cleaning solvent for this use. iBA is reported to rank as the 288th among all the circulated chemicals in Korea, which means it is already regarded as an important chemical, especially in terms of the quantity aspect. In this respect, it is needed to investigate the toxic effects of iBA in experimental animals, and to evaluate the safety with respect to its PEL already set by the OSHA.

Experimental schedule was established in consideration of the working areas: inhalation was applied for 6 hours a day, 5 days a week for 13 weeks. All experimental conditions such as temperature, relative humidity, pressure, air ventilation and illumination cycle in the inhalation chambers were maintained very strictly within the established value±2%. iBA did not induce any decreased activity or abnormal behaviors. Changes in body weight and food consumption during the whole inhalation period did not occur by the inhalation of the iBA. iBA did not induce any abnormal changes in ophthalmic test, urinalysis during and at the terminal of the inhalation toxicity test. Hematocrit, mean corpuscular volume and platelet in the male of 333, 3,000 ppm treated groups were significantly different but not in 1000 ppm group that means they were not correlated with exposure concentration. Red blood cell numbers and hematocrit in the female of 3,000 ppm treated group were significantly increased but others were not. Total protein in the male of all treated groups and albumin of 1,000 and 3,000 ppm treated groups were incresed significantly but not in female groups. These differency were not able to interpret and showed meaningless for there are large range of normal reference values of that parameters (Mitruka *et al.*, 1981). We did not observe any abnormal findings in the gross and microscopic observations due to the inhalation of iBA. There was no alteration in relative organ weights by the inhalation of the iBA. All these results suggest that the levels below 3,000 ppm (the highest level in this experiment) of iBA do not lead to hazardous effects to the health of rats under the inhalation for 13 weeks. Therefore, no observed adverse effect level (NOAEL) of iBA was considered to be more than 3,000 ppm in rats under the inhalation of 6 hours a day, 5 days a week for 13 weeks. These results are in good agreement with other investigators (Klimisch & Hellwig, 1995; Schilling *et al.*, 1997). Limited inhalation studies have indicated a somewhat higher acute toxicity for iBA than for n-butyl alcohol. A 4-hour LC50 of 8,000 ppm has been reported in rats for iBA. The effects of liquid iBA on the human eye appear to be comparable to those of n-butanol but no data are available on ocular exposure to the vapor of iBA.

OSHA formerly had established a limit of 100 ppm as an 8-hour TWA for iBA. But the ACGIH have revised a limit of 50 ppm TWA for this flammable, refractive, colorless liquid. The proposed PEL was 50 ppm as an 8-hour TWA, with which NIOSH concurs. The organization thought that a 50 ppm limit would reduce the significant risk of the skin irritation, which might be associated with the exposure to concentrations at levels above the revised PEL. But in our experiment, we used much higher concentrations

than the already set PEL of 50 ppm, without any harmful effects in all the concentrations. We could argue that 3,000 ppm of iBA is safe enough for rats under this experimental condition simulated to the working places. Extrapolation of animal experimental toxicity data to human is very difficult and disputable. But if considering our experiment was carried out for as long as 13 weeks at the simulated condition of the workers' exposure, our results could be used for suggesting another PEL. If we take the safety factor of 20 rather than usually accepted level of 10 in the field of the inhalation toxicity, then even 150 ppm of iBA, calculated from the NOAEL of 3,000 ppm at the lowest, might not cause any hazardous effects to workers' health. We suspect that 50 ppm of the iBA, the recommended PEL by OSHA, is too low and too conservative even though taking into account the risk of its skin irritation. We suggest that 150 ppm of iBA is safe enough for its PEL in working areas.

REFERENCES

EPA's Stratopheric Protection Division. (1996): Ozone Depletion Glossary, EPA.

Takeuchi Y., Ichihara G. and Kamija M. (1997): A review on toxicity of 2-bromopropane: Mainly on its reproductive toxicity, *J. Occup. Health.*, **39**, 179-191.

Kim, Y.H., Jung, K., Hwang, T., Jung, G. (1996): Hematopoietic and reproductive hazards of Korean electronic workers exposed to solvents containing 2-bromopropane, *Scand. J. Work Environ. Health*, **22**, 387-391.

Park, J. S., Kim, Y., Park, D., Choi, K., Park, S., Moon, Y. (1997): An outbreak of hematopoietic and reproductive disorders due to solvents containing 2-bromopropane in an electronic factory, South Korea: Epidemiological survey, *J. Occup. Health.*, **39**, 138-143.

Appleman L. M., Woutersen R. A. and Freron V. J. (1982): Inhalation toxicity of acetalaldehyde in rat; acute and subacute studies, *Toxicology*, **23**, 293-307.

Bilzer N., Schmutte P., Jehs M., Penners B.M. (1990): Kinetics of aliphatic alcohols (methanol, propanol-1 and isobutanol) in the presence of alcohol in the human body, *Blutalkohol*, **27**(6), 385-409.

Gibel W., Lohs K. H., Wildner G. P. and Schramm T. (1974): Experimental studies on the carcinogenic effect of higher alcohols using 3-methyl-1-butanol, 1-propanol and 2-methyl-1-propanol as examples, *Z. Exp. Chir.*, **7**(4), 235-239.

Hilscher H., Geissler E., Lohs K. H. and Gibel W. (1969): Untersuchungen zur Toxizitat und Mutagenitat einzelner Fuselol-Komponenten an *E. coli, Acta Biol. Med. Germ*, **23**, 843-852.

International Agency for Research on Cancer (IARC) (1985): IARC Monographs on the Evaluation of the carcinogenic risk of chemicals to human. Allyl Compounds, *Aldehyde*, **62**, IARC, Lyon, France.

Kamal M., Abdo Joseph K., Haseman and Abraham Nyska (1998): Isobutyraldehyse administered by inhalation (Whole body exposure) for up to thirteen weeks or two years was a respiratory track toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice, *Toxicological sciences*, **42**(2), 136-151.

Kerns W. D., Pavkov K. L., Donofrio D. J., Gralla E. J. and Swenberg J. A. (1983): Carcinogenesis of formaldehyde in rats and mice after long term inhalation exposure, *Cancer Res.*, **43**, 4382-4392.

Klimisch H. J. and Hellwing J.(1995): Studies on the prenatal toxicity of 3-methyl-1-butanol and 2-methyl-1-propanol in rats and rabbits following inhalation exposure, *Fundam. Appl. Toxicol.*, **27**(1), 77-89.

McKnig B. and Crowley J. (1984): Tests for differences in tumor incidence base on animal carcinogenesis experiments, *J. Am. Stat. Assoc.*, **79**, 639-648.

OSHA: Federal Register, 1989, **54**, 2923.

Schilling K., Kayser M., Deckardt K., Kuttler K., Klimisch H.J. (1997): Subchronic toxicity studies of 3-methyl-1-butanol and 2-methyl-1-propanol in rats, *Hum. Exp. Toxicol.*, **16**(12), 722-726.

Sinclair J., Lambrecht L., Smith E.L. (1990): Hepatic alcohol dehydrogenase activity in chick hepatocytes towards the major alcohols present in commercial alcoholic beverages: Comparison with activities in rat and human liver, *Comp. Biochem. Physiol.*, **96**(4), 677-682.

Woutersen R.A., Appleman L.M., Feron V.J. and van der Heijden C.A. (1984): Inhalation toxicity of acetaldehyde in rats II, Carcinogenicity study: Interim results after 15 monts. *Toxicology*; **31**, 123-132.

Zolotov P.A. and Svintukhovski O.A. (1972): Determination of the maximam permissible concentration of isobutyric aldehyde in the air of the working zone, *Gio. I. Sanit.*, **37**, 104-106.

Brij M. Mitruka and Howard M. Rawnsley (1981): Clinical Biochemical and Hematological Reference Values in Normal Experimental Animals and Normal Humans 2nd Ed. (MASSON Publishing USA, Inc., New York), pp. 58-61, 157-165.