Toxicology Reports 8 (2021) 1839–1845

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Thirteen-week inhalation toxicity study of 1-propanol in F344 rats

Yong-Soon Kim *, Ka-Young Park, Eun-Sang Cho

Chemical Research Bureau, Occupational Safety and Health Research Institute, KOSHA, Daejeon 34122, Republic of Korea

ARTICLE INFO

Handling Editor: Dr. Aristidis Tsatsakis

Keywords:
Inhalation toxicity study
No-observed-adverse-concentration level
Occupational exposure
1-Propanol

ABSTRACT

1-Propanol is a colorless volatile liquid at room temperature and is an important industrial alcohol. Workers are potentially exposed to it through inhalation during industrial activities, including manufacturing, sampling, filling, and mixing processes, as well as during cleaning, maintenance, and repair. Consequently, further information and/or testing for inhalation-related toxicological data is required to assess occupational risk. In this study, 80 (40 male and 40 female) F344 rats were exposed to 1-propanol vapors for 13 weeks (6 h a day, 5 days per week) at target concentrations of 0, 500, 1,600, and 5200 ppm in a whole-body inhalation chamber system. Clinical signs, mean body weight changes, food consumption, hematology, blood biochemistry, necropsy, organ weight, and histopathological findings were observed. The exposure concentrations in chambers were 501.30 ± 9.54 ppm, 1605.43 ± 66.55 ppm, and 5202.19 ± 102.74 ppm for the low, middle, and high dose groups, respectively. No changes related to 1-propanol were observed, including histopathological findings, except for mean body weight changes. The significant decrease in mean body weight at a high dose was not considered to be an adverse effect. Based on these results, the no observed adverse effect concentration of 1-propanol was estimated to be 5202.19 ppm.

1. Introduction

1-Propanol (CAS No. 71-23-8), a colorless volatile liquid at room temperature and normal atmospheric pressure, has a sweet odor and is generally detectable by smell in the range of 2.6–40 ppm; continuous exposure to 1-Propanol likely results in loss of sensitivity to its odor leading to olfactory adaptation [1,2]. It is easily soluble in water and organic solvents [3]. 1-Propanol is an important industrial alcohol, which is a high production volume chemical primarily used in cleaning agents as a solvent in the formulation of disinfectants, pharmaceutical products, cosmetics, coating materials, and enamel, as well as in lacquer paints, printing inks, and paints [1,3–5]. In industrial applications, 1-propanol is used as an intermediate in the synthesis of other chemicals such as n-propylacetate, n-propylformiate, and reactive resins [6,7].

The use of disinfectants, household cleaners, paints, hardener solutions, wall paper removers, kitchen floor cleaners, and so on could expose the general population to the inhalation of 1-propanol. Among these, the use of disinfectants is likely to be the highest contributor; however, exposure due to direct inhalation is very low [1,6]. On the contrary, industrial workers are potentially exposed to the inhalation of 1-propanol during industrial activities including manufacturing, sampling, filling, and mixing processes, as well as during cleaning, maintenance, and repairing [1,3].

The Risk Assessment Report of the Scientific Committee on Health and Environmental Risks of the European Commission presented six scenarios of occupational exposure to 1-propanol: production of propanol and further processing as an intermediate, preparation of formulations, use of paints, use of cleaning formulations, use of printing inks, and use of disinfectants [6].

The primary toxic effects of 1-propanol after a single exposure, include the irritation of mucous membranes and inhibition of the central nervous system, similar to those of ethanol exposure [8], and previous animal studies show that 1-propanol is 2–4 times more intoxicating than ethanol [4,5]. Additionally, previous animal studies conducted according to the guidelines by the Organisation for Economic Co-operation and Development (OECD) are available with the European Chemicals Agency (ECHA), including acute and repeated inhalation studies. However, only a limited amount of data is available at the ECHA website [9], with no acceptable repeated dose studies on inhalation exposure [3]. Furthermore, the Risk Assessment Report suggests that further information and/or testing is needed with regard to 90-day inhalation studies in rats, to perform a robust occupational risk assessment of systemic effects due to repeated dose toxicity [6]. Therefore, in accordance with the OECD Test Guideline No. 413 [10], we performed a

* Corresponding author.
E-mail address: somays@kosha.or.kr (Y.-S. Kim).

https://doi.org/10.1016/j.toxrep.2021.11.004
Received 10 May 2021; Received in revised form 1 July 2021; Accepted 4 November 2021
Available online 6 November 2021

13-week repeated inhalation study to determine the toxic effects of 1-propanol through inhalation exposure, while complying with the principles Good Laboratory Practice (GLP) [11]. This study was supported by the Korea Occupational Safety and Health Agency, Ministry of Labor, Republic of Korea, in the public interest, for the prevention of health hazards in workers.

2. Materials and methods

2.1. Animals

Six-week-old, specific-pathogen-free (SPF) Fischer 344 (F344) rats, including 40 male and 40 female, were purchased from Japan SLC Inc. (Tokyo, Japan) and acclimatized for 7 days in poly-sulfone solid bottom cages (up to three animals of the same sex) with stainless steel grid tops, in an animal room maintained at 22 ± 3 °C, 50 ± 20 % relative humidity, and a 12-h light/dark cycle. The male and female rats weighed 141–173 g and 108–134 g, respectively, before the initial exposure. Thereafter, the animals were housed in whole-body inhalation chambers (1.4 m^3, WITC-14 M, HCT Co., Icheon, Korea) that were maintained at 22 ± 3 °C and 50 ± 20 % relative humidity with individual multi-compartment stainless steel wire mesh cages (W240 × L1200 × H200 mm). The chambers were vented 12 times per hour, and the oxygen concentrations were maintained at a minimum of 19 % during the exposure period. The rats were sustained on an animal diet (18 % protein Rodent Diet 2918C, Envigo RMS Inc., IN, USA) and filtered water ad libitum. This research was approved by the Institutional Animal Care and Use Committee at the Chemical Research Bureau, Occupational Safety and Health Research Institute prior to obtaining the rats, and all the tests were conducted in accordance with the established animal care protocols (Approval No. IACUC-1702).

2.2. Test material, exposure, and analysis

1-Propanol (99.9 % purity) was purchased from REAGENTS DUKSAN (Ansan, Korea). The test material was generated by vaporization, using a liquid vapor generator (LVG-04-A, HCT Co., Icheon, Korea), and gas chromatography (Model No. TRACE1310, Thermo Scientific, MA, USA) was used to analyze its concentration in the inhalation chambers. 1-Propanol was introduced into the chambers by regulating the airflow through the liquid reservoir container in the vapor generator. The chamber concentration of 1-propanol was measured at least three times on each exposure day. During the exposure period, the test material in the liquid reservoir was replaced weekly.

2.3. Test groups

Animals were randomly assigned to four groups (ten animals in each group) in each sex. Each group was exposed to 0 ppm (control, filtered air), 500 ppm (low), 1600 ppm (middle), or 5200 ppm (high) 1-propanol, for 6 h a day, 5 days per week, for 13 weeks. Concentrations for low- and middle-exposure groups were selected based on a previously conducted 28-day study, in which no toxic effects were observed at 100 ppm, 400 ppm, or 1600 ppm, while the high-exposure concentration selected was 5200 ppm, which allowed technically stable exposure and analysis [12,13].

2.4. Clinical observations, body weight, and food consumption

All animals were clinically observed twice (before and after exposure) on the day of exposure and once on the day without exposure for mortality and detailed clinical signs. Individual body weights were evaluated using an electronic balance (QUINTIX3102, Sartorius Co., Göttingen, Lower Saxony, Germany) on the first day of exposure, twice per week in the first 4 weeks, once per week for the remainder of the study, and at the time of euthanasia. Food consumption was individually measured weekly (except on day 57) using the same electronic balance that was used for body weight measurement.

2.5. Hematology and blood biochemistry

After the 13-week exposure, all rats were fasted overnight, and blood samples were collected from the abdominal aorta after anesthesia with isoflurane (Il-sung Pharm, Seoul, Korea); they were sacrificed via exsanguination from the abdominal aorta and vein. The blood samples were prepared in test tubes containing ethylenediaminetetraacetic acid (EDTA) or in serum-separating tubes. Hematological parameters, including white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (HGB) concentration, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT) count, reticulocyte (RET) count, differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), activated partial thromboplastin time (APTT), and prothrombin time (PT) were examined using a blood cell analyzer (ADIVA 2120i, Siemens Diagnostics, Tarrytown, NY, USA) or a coagulation analyzer (ACL Elite Systems, Instrumentation Laboratory, Massachusetts, USA). Blood biochemical parameters, including sodium (Na), potassium (K), chloride (Cl), total protein (TP), albumin (ALB), creatinine (CREA), blood urea nitrogen (BUN), glucose (GLU), calcium (Ca), inorganic phosphorus (IP), total bilirubin (TBIL), total cholesterol (TCHO), triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and albumin/globulin (A/G) ratio were measured using a blood chemistry analyzer (TBA-120FR, Toshiba Co., Tokyo, Japan).

2.6. Necropsy, organ weight, and histopathological examination

All the animals were completely necropsied, which involved the examination of the external body surfaces, all orifices, and the cranial, thoracic, and abdominal cavities and their contents. The weights of the adrenal glands, brain, heart, kidneys, liver, lungs, spleen, testes, thymus, epididymides, ovaries, and uterus were determined after trimming. For histopathological examination, the adrenal glands, aorta, bone marrow, brain, cecum, colon, duodenum, epididymides, esophagus, femur, Harderian glands, heart, ileum, jejunum, kidneys, larynx, liver, lung, lymph nodes (tracheobronchial and mesenteric), mammary glands, nasal cavity, ovaries, pancreas, pituitary, prostate, rectum, salivary glands (submandibular, sublingual, and parotid), sciatic nerve, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, sternum, stifle joint, stomach, teeth, thymus, thyroid, tongue, trachea, urinary bladder, uterus, and vagina were collected and preserved in 10 % neutral buffered formalin. The eyes and testes were collected and preserved in Davidson's fluid. All the preserved tissues from male and female rats of the control and high dosage groups were paraffin-embedded, sectioned with microtome, stained with hematoxylin and eosin, and microscopically examined.

2.7. Statistical analysis

The data obtained during the study period were expressed as mean ± standard deviation (SD). Levene's test was used to test for the homogeneity of group variances, and one-way analysis of variance (ANOVA) was used to compare the means of the groups. If Levene's test was significant, then Kruskal–Wallis non-parametric ANOVA was applied. Dunnett's test or Dunn rank sum test was used following ANOVA as the post hoc test. Pristima® (Version 2.0, Xybion, NJ, USA) was used for all statistical tests. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Concentration in exposure chambers

The analytical concentrations of 1-propanol in the exposure chamber

Table 1
Concentration of 1-propanol in the inhalation chambers during the study period.

Concentration units	1-Propanol			
	Control	500	1600	5200
ppm	0.00 ± 0.00	501.30 ± 9.54	1605.43 ± 66.55	5202.19 ± 102.74
mg/m^3	0.00 ± 0.00	1244.96 ± 23.69	3987.04 ± 165.28	12919.49 ± 255.15

Data are represented as mean ± standard deviation.

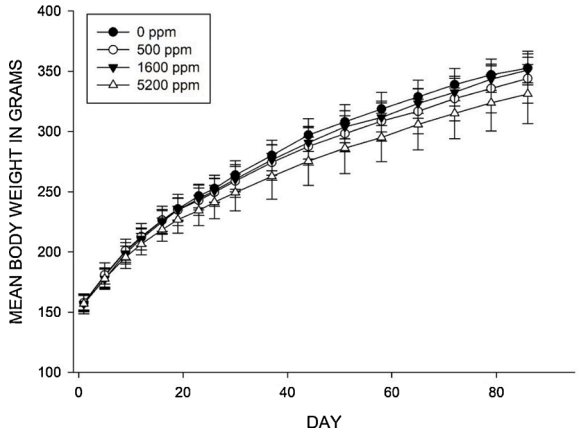

Fig. 1. Changes in mean body weight of male rats after exposure to 1-propanol. Error bars indicate standard deviation. Significant at the 0.05 level (Day 44, 51, 65, 79, and 86 in the high dose group), Significant at the 0.01 level (Day 58 and 72 day in the high dose group).

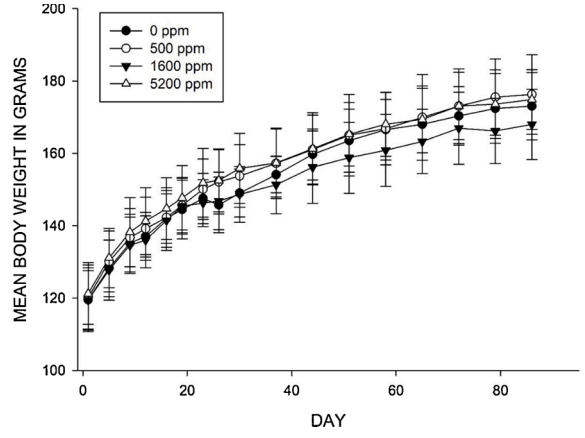

Fig. 2. Changes in mean body weight of female rats after exposure to 1-propanol. Error bars indicate standard deviation. No significant differences were observed.

during the study period for the low, middle, and high dose groups were 501.30 ± 9.54 ppm, 1605.43 ± 66.55 ppm, and 5202.19 ± 102.74 ppm, respectively. When converted to mass units, the analytical concentrations of 1-propanol for the low, middle, and high dose groups were 1244.96 ± 23.69 mg/m^3, 3987.04 ± 165.28 mg/m^3, and 12919.49 ± 255.15 mg/m^3, respectively (Table 1). This conversion was performed using conversion algorithms provided in the OECD guidance document No. 39 [14]. In addition, the delivered high dose was calculated as per male body weight of 300 g and female body weight of 170 g. Calculations were carried out according to the formula presented by Alexander et al. [15], and the IF (proportion by weight of particles that are inhalable by the test species) value was assumed to be "1," because

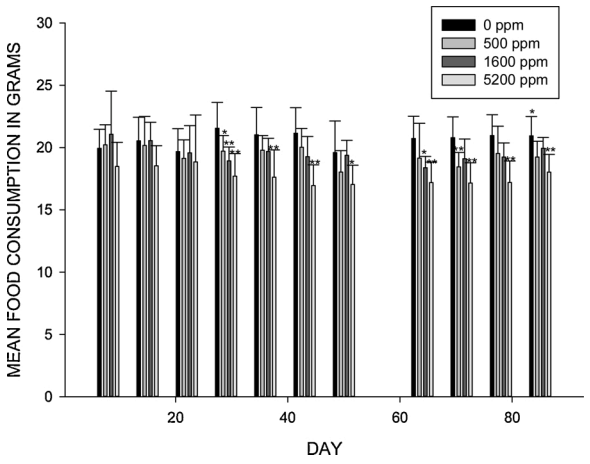

Fig. 3. Changes in mean food consumption of male rats after exposure to 1-propanol. Error bars indicate standard deviation. *, Significant difference from the control group at $p < 0.05$. **, Significant difference from the control group at $p < 0.01$.

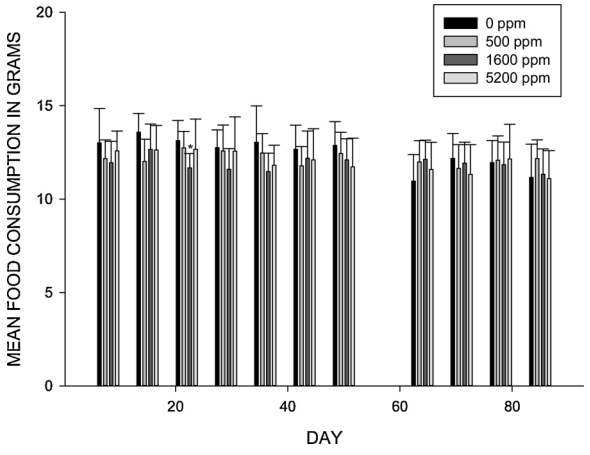

Fig. 4. Changes in mean food consumption of female rats after exposure to 1-propanol. Error bars indicate standard deviation. *, Significant difference from the control group at $p < 0.05$.

1-propanol was in the vapor form. The results of the delivered high doses for male and female rats were 3379.87 mg/Kg/day and 3666.24 mg/Kg/day, respectively.

3.2. Clinical signs, body weight, and food consumption changes

No dead animals and unusual clinical signs (data not shown) were observed, except for one case of soft stools in a male control from day 37 to day 40 after exposure. Significant ($p < 0.05$, $p < 0.01$) decrease in the mean body weight was observed in the male high dose group from day 44 after exposure (Fig. 1); however, no significant changes in weights were observed in the other male and female groups (Fig. 2).

A significant ($p < 0.01$) decrease in food consumption was observed in the male high dose group from day 29 after exposure. In the male low dose group, a significant ($p < 0.05$ or $p < 0.01$) decrease in food consumption was observed on days 29, 71, and 85 after exposure, and in the male middle dose group, a significant ($p < 0.05$, or $p < 0.01$) decrease was observed on days 29, 64, and 71 after exposure (Fig. 3). In the female middle dose group, a significant ($p < 0.05$) decrease in food consumption was observed on day 22 after exposure (Fig. 4).

Table 2
Hematology data of male rats exposed to 1-propanol during the study period.

	1-Propanol (ppm)			
	Control	500	1600	5200
Male (Animal No.)	10	10	10	10
WBC ($\times10^3$/μL)	4.637 ± 0.8498	4.342 ± 0.6718	4.760 ± 0.6724	4.401 ± 0.9490
RBC ($\times10^6$/μL)	8.816 ± 0.1819	8.879 ± 0.1977	9.070 ± 0.1818*	8.818 ± 0.2061
HGB (g/dL)	15.52 ± 0.426	15.79 ± 0.515	15.86 ± 0.386	15.56 ± 0.324
HCT (%)	43.41 ± 0.626	43.87 ± 0.858	44.50 ± 0.818*	43.51 ± 0.931
MCV (fL)	49.3 ± 0.54	49.4 ± 0.51	49.1 ± 0.48	49.3 ± 0.58
MCH (pg)	17.61 ± 0.638	17.78 ± 0.711	17.48 ± 0.561	17.65 ± 0.585
MCHC (g/dL)	35.71 ± 1.029	35.97 ± 1.098	35.65 ± 0.838	35.76 ± 1.043
PLT ($\times10^3$/μL)	680.0 ± 82.83	710.6 ± 37.37	692.6 ± 17.42	596.6 ± 202.84
NEU% (%)	28.11 ± 4.920	25.10 ± 3.641	25.95 ± 6.015	23.98 ± 4.368
LYM% (%)	67.35 ± 5.533	70.29 ± 4.401	69.75 ± 6.185	72.01 ± 4.429
MON% (%)	2.08 ± 0.418	2.10 ± 0.566	1.99 ± 0.390	1.80 ± 0.394
EOS% (%)	1.56 ± 0.448	1.67 ± 0.320	1.60 ± 0.271	1.58 ± 0.270
BAS% (%)	0.16 ± 0.070	0.09 ± 0.032	0.11 ± 0.074	0.13 ± 0.067
RET% (%)	2.536 ± 0.1889	2.527 ± 0.2110	2.421 ± 0.1663	2.324 ± 0.2017
NEUA ($\times10^3$/μL)	1.283 ± 0.2279	1.083 ± 0.1778	1.228 ± 0.2946	1.032 ± 0.1768
LYMA ($\times10^3$/μL)	3.146 ± 0.7285	3.059 ± 0.5586	3.326 ± 0.5938	3.195 ± 0.8002
MONA ($\times10^3$/μL)	0.095 ± 0.0207	0.093 ± 0.0283	0.097 ± 0.0245	0.081 ± 0.0288
EOSA ($\times10^3$/μL)	0.070 ± 0.0176	0.072 ± 0.0132	0.075 ± 0.0165	0.067 ± 0.0134
BASA ($\times10^3$/μL)	0.007 ± 0.0048	0.002 ± 0.0042	0.005 ± 0.0053	0.007 ± 0.0048
RETA ($\times10^9$/μL)	211.23 ± 12.293	218.63 ± 24.522	218.67 ± 20.740	204.90 ± 14.566
APTT (s)	16.49 ± 0.825	17.71 ± 0.918**	17.21 ± 0.582	17.74 ± 0.493**,[a]
PT (s)	10.37 ± 0.323	10.20 ± 0.205	10.36 ± 0.347	10.72 ± 0.427[a]

Data are represented as mean ± standard deviation.
WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet; NEU %, neutrophil relative; LYM%, lymphocyte relative; MON%, monocyte relative; EOS%, eosinophil relative; BAS%, basophil relative; RET%, reticulocyte relative; NEUA, absolute neutrophil; LYMA, lymphocyte absolute; MONA, monocyte absolute; EOSA, eosinophil absolute; BASA, basophil absolute; RETA, reticulocyte absolute; APTT, activated partial thromboplastin time; PT, prothrombin time.
[a] Animal number is 9.
* Significant difference from the control group at $p < 0.05$.
** Significant difference from the control group at $p < 0.01$.

Table 3
Hematology data of female rats exposed to 1-propanol during the study period.

	1-Propanol (ppm)			
	Control	500	1600	5200
Female (Animal No.)	10	10	10	10
WBC ($\times10^3$/μL)	1.894 ± 0.3526	2.603 ± 1.0919	2.191 ± 0.5492	1.735 ± 0.3424
RBC ($\times10^6$/μL)	8.488 ± 0.2937	8.673 ± 0.3226	8.571 ± 0.2855	8.472 ± 0.1755
HGB (g/dL)	16.17 ± 0.587	16.54 ± 0.657	16.43 ± 0.696	16.13 ± 0.794
HCT (%)	43.32 ± 1.177	44.25 ± 1.321	43.56 ± 1.309	43.24 ± 0.989
MCV (fL)	51.1 ± 0.79	51.0 ± 0.50	50.9 ± 0.52	51.0 ± 0.64
MCH (pg)	19.09 ± 1.141	19.06 ± 0.905	19.17 ± 0.865	19.04 ± 0.977
MCHC (g/dL)	37.40 ± 1.610	37.39 ± 1.499	37.70 ± 1.369	37.31 ± 1.524
PLT ($\times10^3$/μL)	780.1 ± 43.39	722.7 ± 77.56	770.2 ± 46.50	756.6 ± 39.11
NEU% (%)	27.19 ± 5.099	29.27 ± 9.545	25.93 ± 4.690	22.33 ± 3.386
LYM% (%)	68.45 ± 5.307	66.29 ± 9.961	69.86 ± 4.661	73.52 ± 3.737
MON% (%)	2.13 ± 0.316	2.40 ± 0.865	2.02 ± 0.577	1.94 ± 0.655
EOS% (%)	1.59 ± 0.292	1.49 ± 0.631	1.43 ± 0.313	1.57 ± 0.283
BAS% (%)	0.16 ± 0.097	0.09 ± 0.057	0.13 ± 0.082	0.07 ± 0.095
RET% (%)	1.814 ± 0.2271	1.957 ± 0.2362	1.822 ± 0.2321	2.026 ± 0.1581
NEUA ($\times10^3$/μL)	0.512 ± 0.1321	0.804 ± 0.5654	0.573 ± 0.2029	0.385 ± 0.0885
LYMA ($\times10^3$/μL)	1.299 ± 0.2753	1.677 ± 0.6416	1.523 ± 0.3648	1.276 ± 0.2767
MONA ($\times10^3$/μL)	0.040 ± 0.0082	0.067 ± 0.0538	0.045 ± 0.0207	0.032 ± 0.0114
EOSA ($\times10^3$/μL)	0.031 ± 0.0074	0.039 ± 0.0197	0.032 ± 0.0140	0.026 ± 0.0070
BASA ($\times10^3$/μL)	0.001 ± 0.0032	0.002 ± 0.0042	0.002 ± 0.0042	0.001 ± 0.0032
RETA ($\times10^9$/μL)	–	–	156.12 ± 20.019	171.79 ± 15.812
APTT (s)	16.10 ± 0.822	16.83 ± 1.141[a]	16.09 ± 1.054	16.58 ± 0.797
PT (s)	10.20 ± 0.432	10.58 ± 0.369[a]	10.69 ± 0.515	10.90 ± 0.521**

Data are represented as mean ± standard deviation.
WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet; NEU %, neutrophil relative; LYM%, lymphocyte relative; MON%, monocyte relative; EOS%, eosinophil relative; BAS%, basophil relative; RET%, reticulocyte relative; NEUA, absolute neutrophil; LYMA, lymphocyte absolute; MONA, monocyte absolute; EOSA, eosinophil absolute; BASA, basophil absolute; RETA, reticulocyte absolute; APTT, activated partial thromboplastin time; PT, prothrombin time.
[a] Animal number is 8.
** Significant difference from the control group at $p < 0.01$.

3.3. Hematology and blood biochemistry

RBC and HCT counts were significantly ($p < 0.05$) elevated in the male middle dose group compared to the male control group, while APTT level was significantly increased ($p < 0.01$) in the male low and high dose groups. PT was significantly increased ($p < 0.01$) in the female high dose group compared to the female control group. No significant changes were observed in other hematological parameters in the male and female rats (Tables 2 and 3).

BUN levels in the male low and middle dose groups were significantly ($p < 0.05$ or $p < 0.01$) elevated, and A/G ratio in the male low and high dose groups was significantly ($p < 0.01$) increased. Additionally, ALP levels in male middle and high dose groups were significantly ($p < 0.05$ or $p < 0.01$) elevated; however, TBIL levels in all male exposure groups were significantly ($p < 0.01$) decreased, compared to the male control group. Na levels in female low and high dose groups were significantly ($p < 0.05$ or $p < 0.01$) increased, and Cl levels in all female exposure groups were significantly ($p < 0.01$) elevated. ALB, TP, TG, and Ca levels in the female high dose group were significantly ($p < 0.05$ or $p < 0.01$) decreased; however, ALP level in the female high dose group was significantly ($P < 0.05$) increased compared to the female control group. No significant changes were observed in other blood biochemical parameters in male and female rats (Tables 4 and 5).

Table 4
Blood biochemical data of male rats exposed to 1-propanol during the study period.

	1-Propanol (ppm)			
	Control	500	1600	5200
Male (Animal No.)	10	10	10	9
Na (mmol/L)	131.54 ± 0.723	131.84 ± 0.578	132.04 ± 0.749	132.04 ± 0.498
K (mmol/L)	3.95 ± 0.200	3.86 ± 0.213	3.92 ± 0.325	4.00 ± 0.309
Cl (mmol/L)	93.37 ± 0.901	93.94 ± 0.830	93.80 ± 1.114	94.27 ± 0.829
TP (g/dL)	6.40 ± 0.141	6.45 ± 0.135	6.48 ± 0.169	6.29 ± 0.183
ALB (g/dL)	4.07 ± 0.095	4.17 ± 0.082	4.15 ± 0.108	4.08 ± 0.109
CREA (mg/dL)	0.514 ± 0.0406	0.529 ± 0.0522	0.527 ± 0.0306	0.534 ± 0.0384
BUN (mg/dL)	16.90 ± 1.636	19.04 ± 1.780*	19.34 ± 1.927**	17.58 ± 1.551
GLU (mg/dL)	182.49 ± 25.240	183.16 ± 26.113	194.19 ± 10.177	189.99 ± 25.559
Ca (mg/dL)	10.89 ± 0.303	10.72 ± 0.365	10.64 ± 0.353	10.52 ± 0.335
IP (mg/dL)	6.17 ± 0.395	6.16 ± 0.851	6.09 ± 0.703	5.97 ± 0.752
TBIL (mg/dL)	0.104 ± 0.0259	0.070 ± 0.0211**	0.072 ± 0.0187**	0.073 ± 0.0187**
TCHO (mg/dL)	82.35 ± 7.473	82.31 ± 8.858	82.91 ± 4.311	80.99 ± 4.291
TG (mg/dL)	104.06 ± 43.264	100.76 ± 39.651	124.34 ± 23.737	117.97 ± 32.775
AST (IU/L)	89.32 ± 10.039	93.27 ± 14.258	86.49 ± 14.802	84.26 ± 5.045
ALT (IU/L)	47.73 ± 4.236	50.23 ± 9.734	48.59 ± 6.652	43.91 ± 3.429
ALP (IU/L)	375.75 ± 32.233	395.90 ± 21.252	413.05 ± 26.273*	421.14 ± 27.305**
A/G ratio	1.75 ± 0.053	1.85 ± 0.097 **	1.79 ± 0.032	1.86 ± 0.053 **

Data are represented as mean ± standard deviation.
Na, sodium; K, potassium; Cl, chloride; TP, total protein; ALB, albumin; CREA, creatinine; BUN, blood urea nitrogen; GLU, glucose; Ca, calcium; IP, inorganic phosphorus; TBIL, total bilirubin; TCHO, total cholesterol; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; A/G ratio, albumin/globulin ratio.
* Significant difference from the control group at $p < 0.05$.
** Significant difference from the control group at $p < 0.01$.

Table 5
Blood biochemical data of female rats exposed to 1-propanol during the study period.

	1-Propanol (ppm)			
	Control	500	1600	5200
Female (Animal No.)	10	8	10	10
Na (mmol/L)	133.50 ± 1.222	134.84 ± 0.877*	134.30 ± 0.884	135.63 ± 0.849**
K (mmol/L)	3.73 ± 0.291	3.74 ± 0.274	3.91 ± 0.206	3.82 ± 0.302
Cl (mmol/L)	96.94 ± 0.803	98.53 ± 0.977**	98.50 ± 0.882**	99.17 ± 0.842**
TP (g/dL)	6.89 ± 0.269	7.05 ± 0.334	6.67 ± 0.200	6.50 ± 0.245 **
ALB (g/dL)	4.36 ± 0.171	4.48 ± 0.175	4.24 ± 0.117	4.14 ± 0.135 **
CREA (mg/dL)	0.519 ± 0.0328	0.536 ± 0.0226	0.511 ± 0.0418	0.507 ± 0.0365
BUN (mg/dL)	23.47 ± 2.166	26.58 ± 3.978	24.27 ± 4.488	22.68 ± 3.403
GLU (mg/dL)	143.04 ± 19.212	137.44 ± 8.248	142.44 ± 16.358	139.03 ± 18.220
Ca (mg/dL)	10.63 ± 0.279	10.60 ± 0.321	10.45 ± 0.143	10.21 ± 0.303**
IP (mg/dL)	5.36 ± 0.781	5.35 ± 0.707	5.78 ± 1.121	5.63 ± 0.865
TBIL (mg/dL)	0.121 ± 0.0202	0.120 ± 0.0200	0.109 ± 0.0160	0.122 ± 0.0204
TCHO (mg/dL)	95.50 ± 8.004	97.33 ± 11.121	86.38 ± 7.694	89.87 ± 9.427
TG (mg/dL)	22.48 ± 9.369	24.19 ± 6.934	15.09 ± 3.541	13.86 ± 5.951*
AST (IU/L)	107.81 ± 17.546	114.24 ± 25.252	95.34 ± 11.906	106.51 ± 24.443
ALT (IU/L)	62.20 ± 37.817	49.49 ± 13.358	44.49 ± 6.317	50.04 ± 16.145
ALP (IU/L)	279.73 ± 25.043	302.15 ± 27.127	303.38 ± 43.341	329.53 ± 46.212*
A/G ratio	1.73 ± 0.048	1.75 ± 0.076	1.75 ± 0.071	1.76 ± 0.070

Data are represented as mean ± standard deviation.
Na, sodium; K, potassium; Cl, chloride; TP, total protein; ALB, albumin; CREA, creatinine; BUN, blood urea nitrogen; GLU, glucose; Ca, calcium; IP, inorganic phosphorus; TBIL, total bilirubin; TCHO, total cholesterol; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; A/G ratio, albumin/globulin ratio.
* Significant difference from the control group at $p < 0.05$.
** Significant difference from the control group at $p < 0.01$.

3.4. Organ weight and histopathological examination

In the male high dose group, the absolute weight of the epididymides and spleen were significantly ($p < 0.01$) decreased compared to the male control group. In the female middle dose group, the relative weights of the kidneys were significantly ($P < 0.05$) increased compared to the female control group. Other absolute and relative organ weights did not show significant changes in either sex (Tables 6 and 7). Microscopic findings such as granuloma of the epididymides; mononuclear cell infiltration of the heart, kidney, liver, lung, and pancreas; mineralization; tubular basophilia and dilation of the kidney; alveolar macrophage aggregates in the lung; pigmentation of the tracheobronchial lymph node; atrophy of the pancreas; cyst in the pituitary gland; basophilic cytoplasmic changes in the salivary gland; hematopoiesis of the spleen; cyst in thyroids; and hemorrhage in the ovary were observed in the control and high dose groups of male and female rats. Although some lesions were observed, they were considered incidental or spontaneous because they were of minimal or mild severity and were commonly observed in similar-aged rats as background lesions.

4. Discussion

Among the general population, 1-propanol is considered to have a low risk, as primary exposure to 1-propanol via inhalation and drinking water is low, and it has minimal environmental impact [1,6,12]. However, workers are potentially exposed, repeatedly for long term, through inhalation during manufacturing, processing, and use of 1-propanol [1]. Furthermore, data for repeated dose toxicity studies are very limited, and the EU Risk Assessment Report proposed that a 90-day inhalation study in rats is needed for further information on the effects on human health [3,6]. Therefore, we performed a 13-week inhalation toxicity study conforming to the OECD Test Guide No. 413 and in accordance with GLP [10,11]. The dosage concentrations in this study were 0, 500, 1600, and 5200 ppm for the control, low, middle, and high dose groups, respectively, based on reference values from previous studies [6,12,13]. No mortality and test substance-related clinical signs were observed during the study period. In the high dose group of males, a decrease in mean body weight and food consumption was observed, which could be attributed to the test substance. With respect to the hematology results, an increase in APTT and PT in rats was not considered to be correlated to the test substance because the changes were minor [16]. The blood biochemistry results in males revealed fluctuations in BUN levels and A/G ratio, that were small and not dose-related. However, a decrease in TBIL level was observed in all the test groups, which seems to be related to the effect of the test substance. Meanwhile, an increase in ALP level was observed in a dose-dependent manner, but no changes in related parameters, organs, and supporting histopathological findings were observed. In female rats, the blood biochemistry results indicated that the changes were only marginally

Table 6
Absolute organ weight of male and female rats exposed to 1-Propanol during the study period.

	1-Propanol (ppm)			
	Control	500	1600	5200
Male (Animal No.)	10	10	10	10
Adrenal glands (g)	0.0490 ± 0.00377	0.0450 ± 0.00447	0.0479 ± 0.00300	0.0466 ± 0.00246
Brain (g)	1.8897 ± 0.04131	1.8611 ± 0.06496	1.8859 ± 0.03013	1.8655 ± 0.05247
Epididymides (g)	1.0138 ± 0.12672	0.9638 ± 0.06016	0.9613 ± 0.02610	0.9032 ± 0.05950**
Heart (g)	0.9384 ± 0.05491	0.8786 ± 0.04950	0.9116 ± 0.05787	0.8782 ± 0.05880
Kidneys (g)	1.9661 ± 0.11107	1.8852 ± 0.10326	1.9532 ± 0.11793	1.8577 ± 0.18838
Liver (g)	9.1322 ± 0.57599	8.8909 ± 0.71229	9.1042 ± 0.48289	8.4697 ± 0.88957
Lung (g)	1.1674 ± 0.02934	1.1483 ± 0.06665	1.1571 ± 0.05282	1.1126 ± 0.06676
Spleen (g)	0.6980 ± 0.03606	0.6842 ± 0.04803	0.6892 ± 0.02456	0.6360 ± 0.03554**
Testes (g)	2.9329 ± 0.12741	2.8800 ± 0.16261	2.9764 ± 0.14120	2.8384 ± 0.13304
Thymus (g)	0.2030 ± 0.01735	0.1997 ± 0.02040	0.1980 ± 0.01918	0.1883 ± 0.01689
Female (Animal No.)	10	10	10	10
Adrenal glands (g)	0.0491 ± 0.00431	0.0452 ± 0.00274	0.0449 ± 0.00453	0.0486 ± 0.00467
Brain (g)	1.7332 ± 0.05793	1.7434 ± 0.03660	1.7186 ± 0.02098	1.7522 ± 0.04331
Heart (g)	0.5323 ± 0.02839	0.5176 ± 0.04289	0.5512 ± 0.06028	0.5507 ± 0.02752
Kidneys (g)	1.0625 ± 0.07544	1.0862 ± 0.06707	1.0788 ± 0.04689	1.1141 ± 0.09064
Liver (g)	4.0620 ± 0.27954	4.1284 ± 0.22560	3.8670 ± 0.17741	3.9651 ± 0.36799
Lung (g)	0.8060 ± 0.07837	0.7960 ± 0.04022	0.7901 ± 0.03896	0.8234 ± 0.07461
Ovaries (g)	0.0565 ± 0.00803	0.0548 ± 0.00649	0.0555 ± 0.00662	0.0537 ± 0.00744
Spleen (g)	0.3613 ± 0.01961	0.3664 ± 0.02640	0.3568 ± 0.02397	0.3624 ± 0.03886
Thymus (g)	0.1579 ± 0.01371	0.1517 ± 0.01634	0.1545 ± 0.00769	0.1614 ± 0.01402
Uterus (g)	0.4332 ± 0.06711	0.4341 ± 0.08971	0.4353 ± 0.10392	0.4246 ± 0.11106

Data are represented as mean ± standard deviation.
** Significant difference from the control group at $p < 0.01$.

Table 7
Relative organ weight of male and female rats exposed to 1-propanol during the study period.

	1-Propanol (ppm)			
	Control	500	1600	5200
Male (Animal No.)	10	10	10	10
Adrenal glands (%)	0.0145 ± 0.00123	0.0137 ± 0.00143	0.0143 ± 0.00082	0.0146 ± 0.00092
Brain (%)	0.5576 ± 0.02530	0.5676 ± 0.02764	0.5620 ± 0.02095	0.5851 ± 0.03851
Epididymides (%)	0.2993 ± 0.04019	0.2939 ± 0.01986	0.2863 ± 0.00816	0.2828 ± 0.01882
Heart (%)	0.2765 ± 0.01011	0.2678 ± 0.01405	0.2713 ± 0.01323	0.2746 ± 0.00927
Kidneys (%)	0.5792 ± 0.01789	0.5742 ± 0.02084	0.5813 ± 0.02545	0.5796 ± 0.02832
Liver (%)	2.6901 ± 0.10886	2.7044 ± 0.09929	2.7099 ± 0.09975	2.6414 ± 0.11622
Lung (%)	0.3443 ± 0.01207	0.3500 ± 0.01892	0.3447 ± 0.01716	0.3481 ± 0.01372
Spleen (%)	0.2057 ± 0.00684	0.2083 ± 0.00919	0.2053 ± 0.00869	0.1990 ± 0.00763
Testes (%)	0.8645 ± 0.02603	0.8773 ± 0.03444	0.8867 ± 0.04576	0.8892 ± 0.05086
Thymus (%)	0.0599 ± 0.00530	0.0609 ± 0.00649	0.0590 ± 0.00602	0.0589 ± 0.00433
Female (Animal No.)	10	10	10	10
Adrenal glands (%)	0.0306 ± 0.00247	0.0277 ± 0.00212	0.0292 ± 0.00322	0.0300 ± 0.00221
Brain (%)	1.0815 ± 0.04345	1.0699 ± 0.04929	1.1194 ± 0.05883	1.0835 ± 0.04901
Heart (%)	0.3319 ± 0.01485	0.3171 ± 0.02211	0.3580 ± 0.03221	0.3401 ± 0.01230
Kidneys (%)	0.6620 ± 0.03116	0.6660 ± 0.03745	0.7019 ± 0.03250*	0.6872 ± 0.03471
Liver (%)	2.5304 ± 0.09693	2.5311 ± 0.12979	2.5147 ± 0.08442	2.4450 ± 0.15770
Lung (%)	0.5023 ± 0.04219	0.4884 ± 0.02973	0.5142 ± 0.02752	0.5079 ± 0.03286
Ovaries (%)	0.0352 ± 0.00449	0.0336 ± 0.00418	0.0361 ± 0.00412	0.0331 ± 0.00362
Spleen (%)	0.2253 ± 0.01049	0.2247 ± 0.01683	0.2318 ± 0.00903	0.2233 ± 0.01545
Thymus (%)	0.0985 ± 0.00906	0.0931 ± 0.01136	0.1005 ± 0.00437	0.0997 ± 0.00847
Uterus (%)	0.2711 ± 0.04783	0.2646 ± 0.04377	0.2823 ± 0.06275	0.2612 ± 0.06365

Data are represented as mean ± standard deviation.
* Significant difference from the control group at $p < 0.05$.

significant, with no changes in related parameters. Likewise, changes in ALP levels were similar to those in males, with no accompanying changes in organs and histopathological findings. The changes in the epididymis, spleen, and kidney weights were small, and no histopathological findings related to the test substance were observed. Moreover, some microscopic findings observed in the epididymis, heart, kidney, liver, lung, pancreas, tracheobronchial lymph node, pituitary gland, salivary gland, spleen, thyroids and ovary were considered incidental or spontaneous lesions [17,18].

The most prominent effects of 1-propanol were suggested to be respiratory tract irritation following high levels of inhalation exposure and hepatotoxic effects at high doses of repeated oral exposure [3,7]. As 1-propanol is rapidly oxidized to its corresponding aldehyde by liver alcohol dehydrogenase (ADH), hepatotoxicity has been predicted [3,4]. However, neither hepatotoxicity nor respiratory tract irritation was observed in our histopathological findings. Contrarily, a significant decrease in mean body weight at a high dose was observed; however, considering that there was no correlation with the test substance in other test parameters, it was inferred that it was not an adverse effect. Therefore, the NOAEC (no observed adverse effect concentration) of 1-propanol was determined to be 5202.19 ppm. This study determined that the inhalation of 1-propanol at technically possible exposure concentrations was not harmful to rats over an exposure period of thirteen weeks. Hence, it can be inferred that harmful effects may not appear even on inhalation of 1-propanol by humans. However, although 1-propanol did not show significant toxicological effects in this subchronic toxicity study, further studies may be needed to analyze the effects of long-term exposure, as observed in workers.

Conflict of Interest

The authors declare no conflict of interest.

Authorship contribution statement

YSK wrote the original draft of the manuscript. YSK, KYP, and ESC contributed to the study planning and editing of the original draft. YSK, KYP, and ESC performed the experiments, and YSK and ESC contributed

to the discussion of data and supervision. All authors have read and approved the final version of the manuscript.

Acknowledgments

This study was supported by the Korea Occupational Safety and Health Agency, Ministry of Labor, Republic of Korea, and a Grant-in-Aid for chemical hazard assessment.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxrep.2021.11.004.

References

[1] International Programme on Chemical Safety (IPCS), (EHC 102), 1-propanol, Environ. Health Criteria 102 (1990).
[2] ACGIH, TLVs® and BEI® based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices, in: Am. Conference of Governmental Industrial Hygienists, Cincinnati, OH, 2007.
[3] European Communities, European Union Risk Assessment Report propa-1-ol, part I, Environment 82 (2008).
[4] United States Environmental Protection Agency (US EPA), Inert Reassessment Document for n-Propanol; Cas No. 71-23–8, Office of Prevention, Pesticides, and Toxic Substances, US EPA, Washington, DC, 2005.
[5] J.L. Unmack, DRAFT 2, n-Propanol; Health-Based Assessment and Recommendation for HEAC, vol. 7, HEAC, Canberra, Australia, 2011.
[6] Scientific Committee on Health and Environmental Risks (SCHER) Risk Assessment Report on PROPAN-1-OL Human Health Part, Cas No. 71-23–8, European Commission, 2008.
[7] J.B. Morris, D.G. Cavanagh, Metabolism and deposition of propanol and acetone vapors in the upper respiratory tract of the hamster, Fundam. Appl. Toxicol. 9 (1987) 34–40, https://doi.org/10.1016/0272-0590(87)90151-5.
[8] M. Vujasinović, M. Koćar, K. Kramer, M. Bunc, M. Brvar, Poisoning with 1-propanol and 2-propanol, Hum. Exp. Toxicol. 26 (2007) 975–978, https://doi.org/10.1177/0960327107087794.
[9] European Chemicals Agency (ECHA), http://ehca.europa.eu/registration-dossier/-/registered-dossier/14586. (Accessed 24 June 2021).
[10] Organization for Economic Co-Operation and Development (OECD), Guideline for the Testing of Chemicals, Section 4, Health Effects Test No. 413 Subchronic Inhalation Toxicity: 90-Day Study, OECD, Paris, France, 2009.
[11] OECD Principles of Good Laboratory Practice, Organization for Economic Co-Operation and Development (OECD), Paris, France, 1998.
[12] E.S. Cho, Y.H. Lee, J.H. Han, S.J. Kim, K.Y. Park, J.M. Jo, S.B. Lee, Evaluation of 1-propanol toxicity in B6C3F1 mice via repeated inhalation over 28 and 90 days, J. Toxicol. 2020 (2020), 9172569, https://doi.org/10.1155/2020/9172569.
[13] Y.S. Kim, E.S. Cho, K.Y. Park, C.H. Lim, Four-week inhalation toxicity study of 1-propanol in F344 rats, Toxicol. Res. 36 (4) (2020) 285–292, https://doi.org/10.1007/s43188-019-00033-1.
[14] OECD Guidance document on inhalation toxicity studies, Series on Testing and Assessment No. 39, 2nd ed., Organization for Economic Co-Operation and Development (OECD), Paris, France, 2018.
[15] D.J. Alexander, C.J. Collins, D.W. Coombs, I.S. Gilkison, C.J. Hardy, G. Healey, G. Karantabias, N. Johnson, A. Karlsson, J.D. Kilgour, P. McDonald, Association of inhalation toxicologists (AIT) working party recommendation for standard delivered dose calculation and expression in non-clinical aerosol inhalation toxicology studies with pharmaceuticals, Inhal. Toxicol. 20 (October (13)) (2008) 1179–1189.
[16] A.W. Hayes, C.L. Kruger, Hayes's Principles and Methods of Toxicology, 2014, pp. 1317–1336. Chapter 26.
[17] A. Brändli-Baiocco, E. Balme, M. Bruder, S. Chandra, J. Hellmann, M. J. Hoenerhoff, T. Kambara, C. Landes, B. Lenz, M. Mense, S. Rittinghausen, H. Satoh, F. Schorsch, F. Seeliger, T. Tanaka, M. Tsuchitani, Z. Wojcinski, T. J. Rosol, Nonproliferative and proliferative lesions of the rat and mouse endocrine system, J. Toxicol. Pathol. 31 (3 Suppl) (2018) 1S–95S, https://doi.org/10.1293/tox.31.1S.
[18] E.F. McInnes, P. Mann, Chapter 2. Wistar and Sprague–Dawley rats. Background Lesions in Laboratory Animals, 2012, pp. 17–36.