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Assessment of Carcinogenicity in Rodents Through Inhalation Exposure to Cyclohexanone

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Abstract

Purpose: Cyclohexanone is a widely used chemical in various industries, and there are concerns about its carcinogenicity to workers in the workplace. Therefore, the purpose of this study is to evaluate the carcinogenicity of cyclohexanone through inhalation exposure.

Methods: In order to evaluate carcinogenicity of cyclohexanone, two species of F344 rat and B6C3F1 mouse were used as experimental animals. For the carcinogenicity test, three exposure groups and a control group were set for each two species. Fifty animals were assigned to each test group, exposure concentrations of 20, 60, and 200 ppm for rats and 50, 150, and 450 ppm for mice were set, 6 h a day, 5 days a week, and the rats were exposed 24 months, mice were exposed for 18 months. Then, the occurrence of exposure-related tumors was analyzed.

Results: In the experimental results, no increase in the incidence of neoplasms or tumors related to exposure to cyclohexanone was observed in either species. From these results, the carcinogenicity of cyclohexanone was not recognized.

Conclusion: We believe that these results could be presented as additional evidence that cyclohexanone does not cause cancer in animals, and that it is not carcinogenic in the respiratory system. Furthermore, we think that it could be presented as additional evidence for the re-evaluation of carcinogenicity classification for cyclohexanone in institutions related to carcinogenicity classification and evaluation.

Keywords: Cyclohexanone; Carcinogenicity; Inhalation; F344 rats; B6C3F1 mice

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Introduction

Cyclohexanone is a chemical substance used in a large amount in various fields as a solvent for semiconductor and LCD manufacturing, a solvent for paint, and other pesticides and cleaners. According to the 2014 field survey of working environment by the Occupational Safety and Health Research Institute (OSHRI) under the Korea Occupational Safety and Health Agency (KOSHA), 586,221 tons of cyclohexanone was used in 869 workplaces, and the number of exposed workers was 98,202. In particular, processes using large amounts were surveyed as manufacturing, reaction, and mixing processes. In addition, according to the 2015 field survey of working environment by the OSHRI, KOSHA, in particular, 15 products containing cyclohexanone were used in 7 places of semiconductor factories. According to the 2019 work environment survey, 1,058 tons of cyclohexanone were used in 1,140 workplaces, and the number of exposed workers was 24,002 people. Therefore, it was investigated that the total usage of cyclohexanone has decreased, but it is still being used in more diverse workplaces.

The concentration levels of cyclohexanone in the working environment were analyzed as 0.273 ppm to 9.743 ppm in the semiconductor, printing and cleaning, medical product assembly, formulation and dispersion in the paint and varnish manufacturing industry, and packing process according to the results of work environment measurement by the Korea Occupational Safety and Health Research Institute in 2010. According to a work environment exposure survey conducted by NIOSH in the United States in 1993, it was found to be 2.8 ppm to 28 ppm in the screen printing process and 0.1 ppm to 2.0 ppm in the paper and vinyl wall cover manufacturing process. The exposure limit of cyclohexanone in Korea is TWA 25 ppm and STEL 50 ppm, and ACGIH is prescribed as TWA 200 ppm and STEL 50 ppm.

Looking at the physicochemical properties of cyclohexanone, it is a colorless and transparent liquid, smells like peppermint or acetone, has a vapor pressure of 5.2 mmHg (25°C) [1], and

has the potential to be exposed through inhalation in a working environment, and has a $logP_{ow}$ of 0.86 (25°C) [2] and is expected to be bioaccumulative ($logP_{ow}$ <1), Viscosity is 2.2 mPa.s (25°C), and the hazard through inhalation exposure is predicted [3].

According to a previous study, cyclohexanone was negative in the reversion mutation test result [4], and the chromosomal abnormality test result did not induce gene mutation in the presence of metabolites, but induction of gene mutations was confirmed in the absence of metabolites [5]. Chromosomal abnormalities were induced in cultured human leukocytes [6,7]. An increase in chromosomal damage was also confirmed in human lymphocytes [8]. Chromosomal abnormalities were induced in male rat bone marrow cells [9]. In addition, a positive result was confirmed in the micronucleus test using mice conducted the Korea Occupational Safety and Health Research Institute in 2013. Therefore, cyclohexanone was considered to be a substance with high carcinogenic potential.

Additionally, the LD50 of cyclohexanone was estimated to be 1.8 mg/kg to 2.11 mg/kg in rats and mice as a result of an acute oral toxicity test. In the case of death, the animals died due to coma, central nervous system depression, and respiratory arrest [10]. In an eye irritation test using rabbits, cyclohexanone was diluted with cottonseed oil and applied to the eyes, and it was determined to be an irritant [11]. In a 13-week repeated oral toxicity study using mice, hyperplasia of the thymus was observed at a dose of 47,000 mg/L [12]. As a result of inhalation exposure to cyclohexanone in rabbits for 3 or 10 weeks, coma, loss of coordination, and mild conjunctival irritation were observed [13]. As a result of intravenous injection of cyclohexanone to beagle dogs for 10 to 21 days, moribund, central nervous system effects, and liver and kidney toxicity were observed [14]. As a result of a 13-week repeated inhalation toxicity test of cyclohexanone in rats and mice, the target organs were identified as the liver and kidney [15].

An allergic contact dermatitis to cyclohexanone was reported in a patch test of 5 patients with paint-related allergies in humans [16]. Irritation of the eyes, nose, and throat was described in a review of volunteers exposed to cyclohexanone [17], and symptoms of liver disease were reported among workers aged 20 to 39 years who were exposed to cyclohexanone for more than 5 years [17].

In experimental animals, the metabolic pathway of cyclohexanone is reduced to cyclohexanol and combined with glucuronide. It has been reported that when cyclohexanone was treated in Wistar and Gunn rats for 28 days, more than 99% of urine metabolites were cyclohexanol glucuronides, and some of cyclohexanone may also be excreted in the bile [18]. In humans, it is mainly metabolized to 1,2- and 1,4-cyclohexandiol-glucuronide, and only a small amount (3.5%) is excreted as cyclohexanol-glucuronide [19]. Therefore, it is thought to be more dependent on cytochrome P450 in humans because it is excreted more in the form of -diol in humans than in experimental animals.

Through this literature review, since cyclohexanone is currently used in large amounts in various industries, there is a high possibility of exposure to workers in the workplace, and it is predicted that the possibility of carcinogenicity is high, carcinogenicity was evaluated through inhalation exposure to cyclohexanone using rodents.

Methods

Test chemical

This test substance, cyclohexanone was purchased from ACROS (Lot No. SNGYB, B2XGG, the Netherlands). It was a colorless liquid with a purity of 99.9% or higher and was stored at room temperature for the duration of the exposure. As a control material, CDA, which is clean air generated from an air handling unit with a HEPA filter and a temperature/humidity control device, was used.

Experimental design

In this study, F344 rats and B6C3F1 mice were used as experimental animals. After receiving rats and mice to this research institute, and after undergoing quarantine and acclimatization period, only animals without abnormalities were used in this study. Experimental animals were classified by 50 animals in each test group based on body weight. According to literature, cyclohexanone has been shown to have effects on central nervous system depression, liver and kidney. In the 90-day repeated inhalation toxicity test in F344 rats, the increase in ALT and AST, and the proliferation of the hepatic bile ducts were observed at the exposure concentrations of 625 and 250 ppm in males. In the kidney, a dose-responsive increase in BUN and an increase in tubular basophilization were observed. Based on these results, in consideration of the exposure period, F344 rats were set at 200 ppm (T3) as the high exposure concentration, and 60 (T2) and 20 ppm (T1) were set as the medium and low concentration exposure groups by applying common ratio 3, respectively. In mice, 450 ppm (T3) was set as a high concentration, and then 150 (T3) and 50 ppm (T1) were set as medium and low concentrations by applying common ratio 3.

Exposure and analytical system

After putting cyclohexanone in a gas generator (LVG-04-A, HCT Co., Korea) connected to a constant temperature water bath set at a constant temperature, clean air was injected to vaporize cyclohexanone. The vaporized vapor was passed through a cooling condenser below room temperature to prevent condensing of cyclohexanone. The vaporized cyclohexanone and clean air were mixed and supplied into the whole-body exposure chamber with a size of 5 m^3 (rat) or 1.4 m^3 (mouse) at the set exposure concentration.

The concentration of cyclohexanone in each exposure chamber was analyzed by gas chromatography (Trace 1300, Thermo Fisher Scientific Co., USA) through an air sampling device connected to the respiratory area of the experimental animal. Analysis was performed at least 3 times for each exposure concentration per day during the exposure period.

Animals

F344 rats and B6C3F1 mice were purchased from Japan SLC, Inc. (Shizuoka, Japan). These species were selected for the study because these animals are generally used in carcinogenicity studies and the availability of considerable background information for these species. The animals were obtained at 5 weeks of age and acclimated and quarantined for 2 weeks.

During the exposure period of the test substance, all animals were housed individually in stainless-wire mesh cages (230 mm [W] × 1200 mm [L] × 200 mm [H] for rats and 220 mm [W] × 600 mm [L] × 150 mm [H] for mice) in the chambers set at a temperature of 22 ± 3°C, relative humidity of 50 ± 20%, illumination of 150~300 Lux, and ventilation frequency of 10~20 times/h. All animals were fed rodent diet (Teklad Certified Irradiated Global 18% Protein Rodent Diet, Envigo Co. Ltd., USA), and water was ad libitum filtered and UV-sterilized tap water. These studies were approved by the Institutional Animal Care and Use Committee.

Table 1: Concentrations of cyclohexanone in the inhalation chambers for exposure period.

Chamber	Group		Concentration (ppm)	*Differences concentration (%)	#Variation index
Rat	T1	N	522	0.15	6.28
		Mean	20		
		Sdevs	0.84		
	T2	N	522	0.51	4.83
		Mean	60.27		
		Sdevs	2.56		
	T3	N	522	1.83	4.74
		Mean	204.07		
		Sdevs	8.55		
Mouse	T1	N	387	-0.28	6.8
		Mean	49.86		
		Sdevs	3.39		
	T2	N	387	-0.18	7.93
		Mean	149.73		
		Sdevs	11.88		
	T3	N	387	1.26	4.397
		Mean	455.68		
		Sdevs	22.67		

*: [found concentration - intended concentration]/intended concentration × 100
#: Standard deviation/mean value × 100

Observations, analysis, and histopathological examinations

During the exposure period of the test substance, all animals were observed daily for clinical signs and mortality, and body weight and feed intake were measured once a week until 13 weeks, and then once every 4 weeks thereafter.

The following organs were removed from died or survived animals during the exposure period and fixed in 10% neutral buffered formalin solution to perform histopathological examination of tumors: Abnormal lesions, ovaries, adrenals, pancreas, parathyroids, aorta, pituitary, bone marrow, preputial glands, brain, prostate, cecum, rectum, clitoral glands, salivary glands (submandibular, sublingual, parotid), coagulating glands, colon, salivary glands, duodenum, sciatic nerves, epididymides, seminal vesicles, esophagus, skeletal muscle, eyes, skin, femur, spinal cords, gall bladder (mouse only), spleen, harderian glands, sternum, heart, stifle joint, ileum, stomach, jejunum, teeth, kidneys, testes, lacrimal glands, thymus, larynx, thyroids, liver, tongue, lung, trachea, lymph node (mesenteric), urinary bladder, mammary gland, uterus, nasal cavity, vagina, optic nerves, zymbal glands, lymph node (tracheobronchial).

Statistical analysis

Data collected during the test period were expressed as arithmetic mean and standard deviation per test group, and statistical analysis of the collected data was performed using Pristima 7.1.0 and IBM SPSS Statistics 26.

For data on body weights and feed intakes, after Levene's test and one-way ANOVA, Dunnett LSD test was performed to compare differences between test groups in case of equal variance. If the variance was not equal, the Kruskal-Wallis test was performed, and then Dunn Rank Sum test was performed as a post hoc test.

The survival rate of experimental animals was analyzed by Kaplan-Meier analysis, and Log Rank test was performed to compare the survival curves of the control group and the test group. And the analysis of the occurrence of the tumor was analyzed using the Poly-3 test. Non-neoplastic findings were compared between test groups using Fisher's Exact Test.

Results

Exposure concentration

The concentrations of cyclohexanone in the inhalation chamber measured during the exposure period are described in Table 1. The average concentration of cyclohexanone in the chamber for rats was measured as 20.03 ± 1.26, 60.31 ± 2.91, and 203.66 ± 9.66 ppm, respectively. The difference concentration [(found concentration-intended concentration)/intended concentration × 100] was 0.17% to 1.83%, and the variation index (standard deviation/mean value × 100) was 4.74% to 6.28%. The average concentration in the mouse chamber was measured as 49.86 ± 3.39, 149.73 ± 11.88, and 455.68 ± 22.67 ppm, respectively, the difference from the set concentration was -0.28% to 1.26%, and the coefficient of variation was 4.97% to 7.93%. Therefore, it is judged that each experimental animal has been exposed to the target concentration of the test substance.

Mortality

The dead animals during the exposure period are shown in Figure 1, 2.

Rats

For male rats during the exposure period of the test substance, the number of deaths (mortality rate) and the average lifespan of each test group were 41 (82%) and 527.9 days in the control group, 43 (86%) and 509.2 days in the 20-ppm exposure group, 36 (72%) and 612.3 days in the 60-ppm exposure group, and 40 (80%) and 543.2 days in the 200-ppm exposure group. The number of deaths (mortality rate) and the average lifespan of each test group in female rats were 21 (42%) and 635.9 days in the control group, 24 (48%) and 630.5 days in the 20-ppm exposure group, 31 (62%) and 624.4 days in the 60-ppm exposure group, and 24 (48%) and 619.3 days in the 200-ppm exposure group.

Mouse

In the case of male mice during the exposure period of the test substance, the number of surviving individuals (survival rate) and average lifespan in each test group were 48 (96%) and 539.3 days in the control group, 48 (96%) and 536.8 days in the 50-ppm exposure group, 48 (96%) and 543.8 days in the 150-ppm exposure group, and 47 (94%) and 531.5 days in the 450-ppm exposure group. The number of survivors (survival rate) and mean lifespan of each test group in the case of female rats were 46 (92%) and 537.0 days in the control group, 46 (92%) and 524.5 days in the 50-ppm exposure group, 43 (86%) and 525.8 days in the 150-ppm exposure group, and 46 (92%) and 541.6 days in the 450-ppm exposure group.

Neoplastic and non-neoplastic lesions

The results of representative neoplastic findings in this study are presented in Table 2, 3. As a result of Poly-3 analysis of the frequency of tumor occurrence, statistically significant changes were observed in the test substance-exposed groups compared to the control group in the testicular adenoma of Leydig cells of the male rats and the adenoma of Harderian glands of the female mouse.

As non-neoplastic findings, duct dilatation of the clitoral gland and

Table 2: Incidence of neoplasms after inhalation of cyclohexanone on the rats.

Organs	Findings Number of animals examined	Male				Female			
		C	T1	T2	T3	C	T1	T2	T3
		50	50	50	50	50	50	50	50
Lung	Adenoma, bronchioloalveolar	0	0	0	0	2	1	0	2
Adrenals	Pheochromocytoma	3	1	2	4	0	1	0	0
Pituitary	Adenoma, pars distalis	16	13	17	12	20	18	16	19
	Carcinoma, pars distalis	0	1	1	0	1	0	0	1
	Adenoma, pars intermedia	0	0	0	1	0	1	0	2
Spleen	Leukemia, lymphocyte	13	4	10	12	8	4	3	11
	Leukemia, NOS	4	9	5	6	1	1	5	3
	Leukemia, erythroid	0	2	1	1	0	0	2	1
	Leukemia, myeloid	0	2	0	0	0	1	0	0
Thyroids	Adenoma, follicular cell	1	2	0	1	1	2	0	0
	Adenoma, C cell	2	0	1	1	2	0	0	2
	Carcinoma, C cell	0	0	0	1	0	1	1	0
	Carcinoma, follicular cell	0	1	0	1	0	0	0	0
	Neoplasia, NOS	0	0	0	0	1	0	0	0
Testes	Adenoma, Leydig cell	19	9*	13*	11	-	-	-	-
Mammary	Adenoma	-	-	-	-	1	1	0	2
gland	Adenocarcinoma	-	-	-	-	0	0	1	1
	Fibroadenoma	-	-	-	-	4	4	6	8

*: Poly-3 test Significant at the 0.05 level

Table 3: Incidence of neoplasms after inhalation of cyclohexanone on the mice.

Organs	Findings Number of animals examined	Male				Female			
		C	T1	T2	T3	C	T1	T2	T3
		50	50	50	50	50	50	50	50
Lung	Adenoma, bronchioloalveolar	4	1	2	4	0	0	0	3
	Carcinoma, bronchioloalveolar	1	1	0	0	0	0	0	1
Adrenals	Adenoma, subcapsular cell	1	0	0	2	0	0	0	0
Harderian	Adenoma	2	3	4	4	7	1*	1*	1*
gland	Adenocarcinoma	1	0	1	0	0	1	0	0
Liver	Adenoma, hepatocellular	7	11	8	10	1	0	1	2
	Carcinoma, hepatocellular	11	8	8	5	1	1	0	0
	Hemangioma	1	0	2	0	0	0	0	0
	Neoplasia, NOS	0	0	0	0	0	0	1	0
Thyroids	Adenoma, follicular cell	1	0	1	0	0	0	0	0
	Adenoma, C cell	0	0	0	1	0	0	0	0
	Carcinoma, C cell	0	0	0	0	0	0	1	0

*: Poly-3 test Significant at the 0.05 level

increase in femur and sternum bone showed a statistically significant decrease in female rats exposed to 200 ppm of cyclohexanone compared to the control group. In mice, Mineralization of brain, renal cyst and tubular basophilia showed statistically significant changes in males exposed to 450 ppm. In females, the hyaline cast of the kidney showed a statistically significant increase in the 450-ppm exposure group (data not shown).

Discussion

This study was conducted to evaluate carcinogenicity through repeated inhalation exposure to cyclohexanone using F344 rats and B6C3F1 mice.

During the exposure period of the test substance, there was no decrease in survival rate compared to the control group in all test substance-exposed groups of rats and mice.

In the case of rats, the tumorigenicity in dead or moribund animals were identified as macro granulocyte leukemia, unspecified leukemia, anterior pituitary adenoma in males and females, and mammary gland fibroadenoma in females. These tumors are considered to be spontaneous tumors in F344 rats [20]. The main cause of non-tumorigenicity in dead or moribund animals was necrosis with

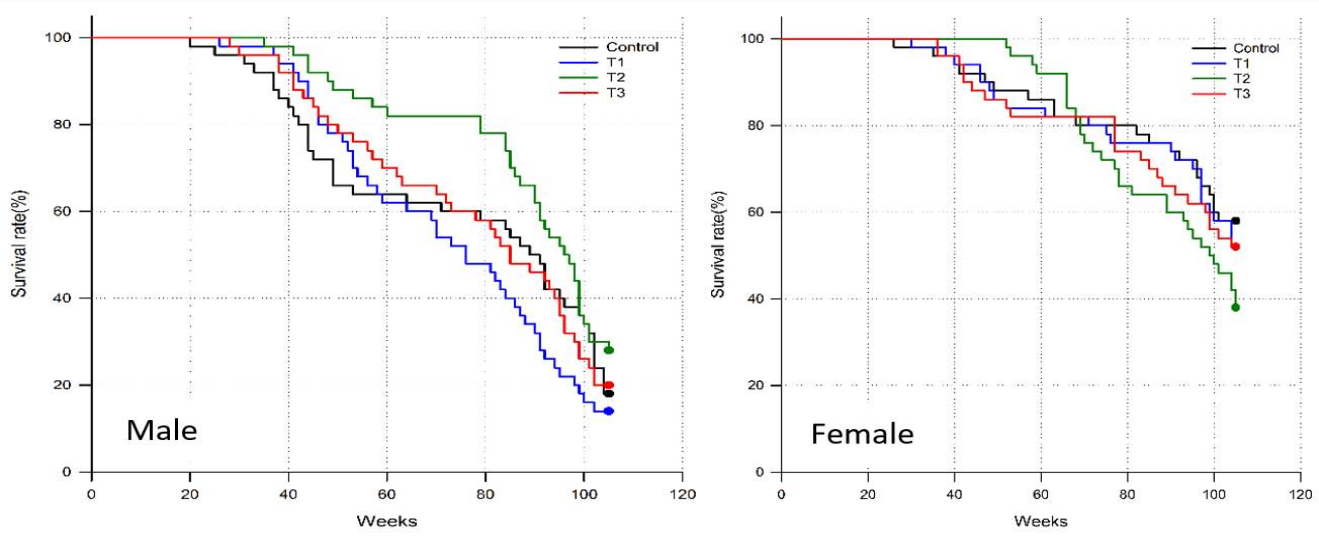

Figure 1: Adjusted percentage Kaplan-Meier survival curves for F344 rats exposed to cyclohexanone by inhalation for 104 weeks. There was no statistically significant difference in the results of the Log Rank test to compare the survival rate with the control group.

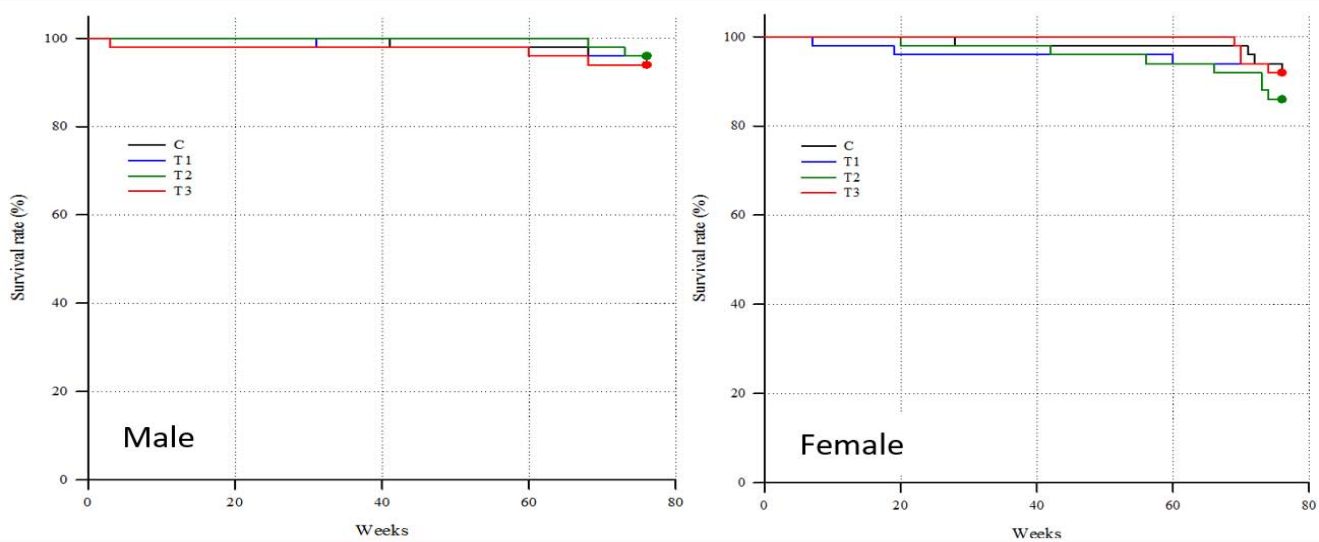

Figure 2: Adjusted percentage Kaplan-Meier survival curves for B6C3F1 mice exposed to cyclohexanone by inhalation for 78 weeks. There was no statistically significant difference in the results of the Log Rank test to compare the survival rate with the control group.

inflammation and hemorrhage of the mucous membranes in the bladder as incidental infection, and broken teeth were judged to be the cause of death or moribund due to the inability to eat feed, resulting in deterioration of general health. In addition, the other died animals were judged to be accidental accidents not related to the test substance exposure. Although the survival rate was low due to these causes, there was no statistically significant difference in mortality between the test substance exposure group and the control group, so it was not judged as an effect related to the test substance exposure. In the case of mice, some individuals died, but the dead animals from specified tumor were not identified, so it was not considered to be an effect of the test substance.

The adenoma of Leydig cells observed in male testis of rats exposed to exposure concentrations of 20 and 60 ppm of test substances are a common tumor observed in F344 rats at the corresponding week of age [21], and it was judged that there was no toxicological significance because the frequency of occurrence decreased in the exposed group.

Duct dilatation of the clitoral gland and increase in femur and sternum bone were decreased in female 200 ppm exposed group. These changes are also spontaneously occurring lesions commonly observed at the age of the F344 rats [22,23], and the frequency of occurrence decreased in the test substance exposure group, so it was judged that there was no toxicological significance. In addition, the observed findings were all spontaneously occurring and were judged to have no toxicological significance because they were distributed accidentally or sporadically.

In mice exposed to cyclohexanone, there were also no exposure-related neoplastic findings. However, the adenoma of Harderian gland of the female mice was decreased in all exposed groups compared to the control group. Since this is a tumor commonly observed at that age [22], it was judged that there was no toxicological significance. The other findings in mice were spontaneously occurring lesions, and

they occurred incidentally or sporadically, and were judged not to be related to the test substance exposure.

In the literature on the carcinogenicity of cyclohexanone, six males with thyroid adenoma-carcinoma were observed in the high-dose (6500 ppm) group in the carcinogenicity study, in which cyclohexanone was mixed with drinking water and orally administered to F344 rats for 2 years [24]. However, because the non-genetic mechanism of thyroid tumorigenesis is currently considered to have little or no relevance in humans exposed to relatively low levels of the chemical, it is classified as A3 in the ACGIH [25,26]. In addition, the frequency of tumor occurrence in this study was not determined to be related to cyclohexanone exposure due to the change in the background lesion and the lack of a dose-response relationship.

Studies on the genotoxicity of cyclohexanone so far have been summarized and adequately documented in the German Commission for Health Risk Investigation of Chemicals in the Workplace in 1994 [27] and IARC in 1999 [28]. In these studies, the results were mainly negative. Currently, cyclohexanone is classified in Group 3 by the IARC as "not classifiable for carcinogenicity in humans".

Conclusion

In conclusion, as a result of exposure to cyclohexanone in F344 rats and B6C3F1 mice to evaluate the carcinogenicity of cyclohexanone through inhalation exposure, cyclohexanone exposure-related tumor development was not confirmed in both species. We believe that these results could be presented as additional evidence that cyclohexanone does not cause cancer in animals, and additionally as evidence that cyclohexanone is not carcinogenic to the respiratory system. Furthermore, we believe that the carcinogenicity classification of cyclohexanone classified as A3 by ACGIH could be presented as evidence for re-evaluation.

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