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A Twenty-Eight Days Inhalation Toxicity Study of N-decane in Sprague Dawley Rats

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SD 흰쥐를 이용한 n-decane의 28일 반복흡입독성연구

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요 약

N-decane은 지방족탄화수소로 다른 탄환수소들과 같이 혼합된 형태로 존재하며 페인트 제거제나 드라이 크리닝 제품에 사용된다. 최근의 본 연구팀이 실시한 전자산업계의 MSDS 신뢰성조사 결과에 따르면 세정제의 사용 경향은 과거의 방향족 탄화수소나 CFC, HCFC에서 C_{10} 이상의 지방족탄화수소 물질로 변화되고 있는 경향을 보여주었다. Stoddard solvent나 나프타 같은 탄화수소 혼합물에 대한 작업 환경노출기준은 설정되어있지만 n-decane에 대해서는 제한적인 독성자료 밖에 없으며 작업환경노출기준은 설정되어 있지 않다. 따라서 작업환경에 대한 적절한 관리기준제시와 독성학적 자료를 제공하기 위해 n-decane을 28일 반복 흡입독성시험을 실시하였다. 6주령 흰쥐로 체중이 229±10 g되는 숫컷과 165±7 g되는 암컷 흰쥐를 4개 용량군 즉 대조군, 저농도군(50 ppm), 중농도군(200 ppm), 고농도군(800 ppm) (각군당 10마리)으로 설정하여 하루 6시간, 주5일로 4주간 흡입챔버에서 노출시켰다. 28일간 노출 후 n-decane의 노출용량에 따른 암수의 체중에는 유의한 변화가 없었으며 유의한 혈액학적 생화학적 변화도 발견되지 않았다. 고농도로 노출된 수컷 몇 마리에서 고환 세정관에서의 공포화(vacuolization)가 발견되었으나, 간, 신장, 비장, 폐, 부신, 심장, 뇌 등 다른 장기에 대한 조직병리학적 검사에서는 뚜렷한 조직병리학적인 변화를 발견할 수 없었다.

Key words : N-decane, aliphatic hydrocarbon, inhalation, cleaning solvent

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INTRODUCTION

N-decane (CAS No. 124-18-5), an aliphatic hydrocarbon found in cleaning solvents as a mixture with other hydrocarbon, has been used in paint removers and dry-cleaning products (Wallace *et al.*, 1989; Tashiro *et al.*, 1999). Our previous study on the reliability of Material Safety Data Sheets (MSDS) for chemicals mixtures in the electronic industry revealed that the use of cleaning solvents is shifting from widely used aromatic hydrocarbons, CFCs, or HCFCs, to aliphatic hydrocarbons or n-paraffins with longer than C_{10} (Yun *et al.*, 2000). The benefits of using the aliphatic hydrocarbon or n-paraffin solvents are: (1) they are regarded as less hazardous than aromatic hydrocarbons; thus they are recommended as substitutes for the aromatic hydrocarbons (Filskov *et al.*, 1996); and (2) they have less regulatory requirements for employees. Because CFCs and HCFCs are regulated as ozone-destroying chemicals, they are recommend or required to be removed from industrial operations. Because they don't have specific occupational exposure levels, use of $C_{10} \sim C_{15}$ aliphatic hydrocarbons would not require employees to monitor occupational exposure levels. Although there are occupational exposure levels for the aliphatic hydrocarbon, including Stoddard solvent (CAS No. 8052-42-3) and naphthas (8032-32-4, 8030-30-6) (ACGIH, 2000), they are not applicable in real exposure monitoring situations because it is difficult to evaluate exposure of mixture chemicals. Only limited data for the toxicity of n-decane were available. N-decane had LC 50 of 72300 mg/m^3/2 hours in mice, 912 mg/kg of the lowest lethal dose, and 25 g/kg/52 weeks of the lowest lethal dose, and was classified as a tumorigen in NIOSH RTEC (1997)

Because n-decane has not been widely used as a major component in cleaning-solvent mixtures in the electronic industry, and because its toxicity data were not available to give proper measures for the workplace, we examined possible toxicity of n-decane through a 28-day for inhalation toxicity experiment to provide the supportive toxicity data for n-decane.

MATERIALS AND METHODS

1. Chemicals

N-decane was purchased from Junsei Chmical Co. (Japan)

2. Animals and conditions

Five-week-old male and female, specific pathogen-free (SPF) Sprague-Dawley rats were purchased from Daehan Animal Center (Korea) and were acclimated for 1 week before the start of experiments. During the acclimation and experimental periods, rats in polycarbonate cages (5 rats per cage) were housed in a room with controlled temperature (23 ± 2°C) and humidity (55 ± 7%) with 12 hr light/dark cycle. Rats were fed Purina rodent chow (Ralston Purina Co., St Louis, MO) and filtered water *ad libitum*. Six-week-old rats weighing about 229 ± 10 g for male and 165 ± 7 g for female were placed in to four groups (10 rats in each group); fresh air control, low-dose group (50 ppm), middle-dose group (200 ppm), and high-dose group (800 ppm). The animals were exposed to n-decane 6 hours each day, 5 days per week, for 4 weeks. Animals were examined daily during weekdays for evidence of any treatment-related effects, including respiratory, dermal, behavioral, nasal or genitourinary changes suggestive of irritancy. Body weights were evaluated at the time of purchase, grouping, twice a week after the inhalation of the exposure and before necropsy.

3. Exposure atmosphere generation

Inhalation exposures were conducted in Sibata SIS-20RG stainless steel whole-body exposure chambers. Rats were housed in separate chambers during the study. Animal cages were rotated weekly to reduce any variation in the levels of n-decane by the animals. Four chambers, each containing 20 animals (10 male and 10 female), were used. Each

chamber reflected different exposure levels, including controls. Chamber flow rates were maintained between 211.2~211.3 l/min and 12.67~12.80 air changes per hour. Flow rates, temperature, humidity, and pressure in the chambers were monitored every 30 minutes by a sensor and environment controller (Sibata, ICS-20RG, Japan), and recorded. Chambers were maintained between 21 and 23°C. Humidity ranged from 40 to 49% with overall means ranging from 43.8 to 45.1%.

N-decane vapor was generated by a gas generator (FG-4R, Sibata, Japan) then mixed with fresh air to supply to the exposure chambers. Concentration of n-decane was monitored every 15 min by a gas chromatograph (flame ionization detector, GCS-14PFFS, Shimadzu, Tokyo), equipped with auto-sampler. The column was silicon DC-200 15% Chromosorb (AW-DMCS, Shimadzu, Tokyo), 80/100 mesh, and 0.5 m. Oven, detector, and injection temperatures were 190, 280 and 280°C, respectively. The concentrations of n-decane in the exposure chambers were 47±6.42 ppm for the low-dose, 201.8±6.42 ppm for the middle-dose, and 800±22.38 ppm for the high-dose group.

4. Biochemistry and hematology

At the conclusion of 4-week experiment, rats were 10 weeks old. Before necropsy, rats were fasted for 24 hours and anesthetized with ether. Blood was drawn from abdominal aorta and collected into heparinized vacutainers. It was then then analyzed for aspratate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), glucose (GL), urea nitrogen (BUN), total protein (TP), total cholesterol (TCHO), creatinine (CRTN) and total bilirubin (TB) using a biochemical blood analyzer (model TBA-20FR, Toshiba, Japan). The blood was analyzed also for red blood cell counts (RBC), white blood cell counts (WBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and platelet counts (PLT) using a blood cell counter (Sysmex F-820, Toa Medical Electronics Co., Kobe, Japan).

5. Organ weights and histopathology

After collecting the blood, rats were sacrificed by cervical dislocation. Adrenal glands, testes, epididymis, heart, lungs, kidneys, spleen, liver and brain were removed carefully. These organs were weighed and fixed in a 10%-formalin solution containing neutral phosphate buffered saline. All organs were fixed, embedded in paraffin, stained with hematoxylin and eosin, and examined under light microscopy.

6. Statistical analysis

Multiple variance analysis and Duncan's multiple range tests were used to compare the body weights, organ weights, results of blood biochemistry and hematology obtained from the three experimental groups with those obtained from the fresh air control rats.

RESULTS

1. Animal observation

One case of mild hair loss was found in the low- and high-dose group of male rats, and one and two cases of mild hair loss were observed at the low- and high-dose group of female rats, respectively. The localized hair losses were distributed from the head to the shoulder and the back.

2. Effects on body weights and organ weights

The ranges of n-decane concentrations to rats were based on its saturation concentration. The highest vapor concentration of n-decane in our experiment was over 60% of the saturation concentration. Higher than 1,000 ppm of n-decane was not attainable by our inhalation system. Male and female rats did not show any significant changes in body weight depending on the concentration of n-decane during the 28 days of

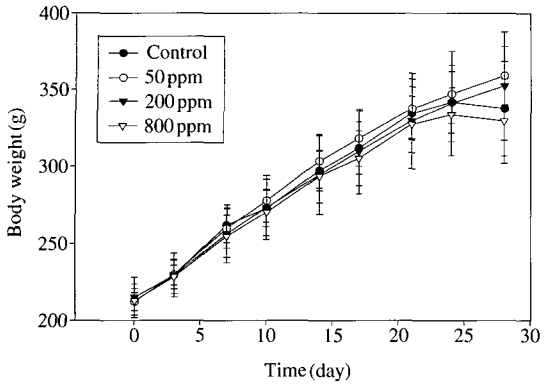

Fig. 1. Body weight changes of male rats during 28 days of n-decane exposure. Male rats were exposed to fresh air control (filled circles), 50 ppm (open circles), 200 ppm (closed triangles), and 800 ppm (open triangles) of n-decane for 28 days. Ten male rats were assigned to each exposure group. Body weight was measured at the time of grouping and twice a week after the initiation of the exposure.

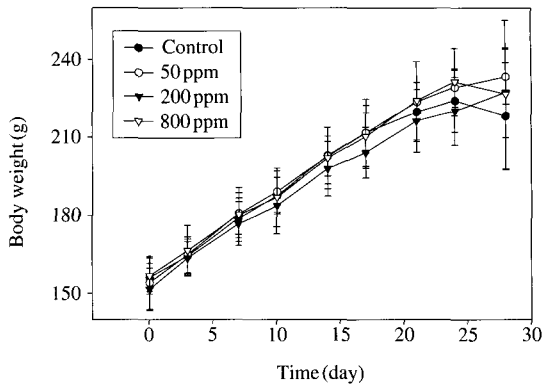

Fig. 2. Body weight changes of female rats during 28 days of n-decane exposure. Female rats were exposed to fresh air control (filled circles), 50 ppm (open circles), 200 ppm (closed triangles), and 800 ppm (open triangles) of n-decane for 28 days. Ten female rats were assigned to each exposure group. Body weight was measured at the time of grouping and twice a week after the initiation of the exposure.

Table 1. Body and organ weights of male rats exposed to n-decane for 4 weeks

	Control (10)	Low (10) 50 ppm	Middle (10) 200 ppm	High (10) 800 ppm
Body weight (g)	315±26	336±19	329±34	307±26
† Organ weights (mg/100 g)				
Adrenal (R)	7.8±1.3	7.8±1.7	7.8±1.4	8.4±1.7
Adrenal (L)	7.5±1.7	7.4±1.4	7.5±1.2	8.1±1.5
testis (R)	529±66 [1653±170]	482±22 [1619±99]	485±46 [1585±83]	492±29 [1511±141]
testis (L)	524±57 [1659±166]	474±30 [1593±109]	483±44 [1576±70]	499±38 [1531±135]
heart	347±24	333±14	330±28	352±53
lung (R)	273±31	256±28	248±15*	258±22
lung (L)	135±13	130±8	133±11	135±16
kidney (R)	389±32	391±34	398±42	403±44
kidney (L)	382±31	391±26	383±35	400±32
spleen	225±18	250±28*	243±28	225±34
liver	3115±277	2966±312	3081±192	3108±330
brain	648±61	572±102	618±59	665±46

The numbers in parenthesis indicate the number of rats. *indicates significant difference at $p<0.05$. [ ] indicates absolute organ weight. † All organ weights were normalized to mg/100 g of body weight.

the experiment (Figs. 1 & 2).

Besides a slight decrease in the right lung weight in the middle dose group and a slight increase of spleen weight in the low-dose group in male rats, no significant organ weight changes were observed in either male and female rats after 28 days of n-decane exposure (Table 1 & 2). The weights of male and female reproductive system showed a slight dec-

Table 2. Body and organ weights of female rats exposed to n-decane for 4 weeks

	Control (10)	Low (10) 50 ppm	Middle (10) 200 ppm	High (10) 800 ppm
Body weight(g)	202±18	215±8	210±15	209±26
ǂ Organ weights (mg/100 g)				
Adrenal (R)	16.2±1.7	14.8±1.7	15.8±2.2	14.6±3.1
Adrenal (L)	16.0±0.8	13.9±2.6	15.2±2.3	15.1±2.7
Ovary (R)	42.0±11.0 [83±17]	34.7±6.8 [74±14]	37.9±10.8 [77±21]	37.9±10.5 [78±14]
Ovary (L)	43.3±10.5 [86±15]	34.7±4.0 [73±8.4]*	35.0±5.2 [73±8.5]*	36.8±7.4 [75±10]
heart	382±37	371±12	371±20	386±35
lung (R)	317±24	334±30	317±24	258±22
lung (L)	177±17	167±14	166±9	169±13
kidney (R)	377±18	376±21	370±25	382±17
kidney (L)	379±26	378±18	375±27	375±23
spleen	261±42	259±34	248±23	244±34
liver	2932±330	2881±162	2894±133	3020±289
brain	922±80	896±35	919±76	928±123

The numbers in parenthesis indicate the number of rats. *indicates significant difference at $p<0.05$. [ ] indicates absolute organ weight. ǂ All organ weights were normalized to mg/100 g of body weight.

Table 3. Hematology data of male rats treated with n-decane

	Control (9)	Low (10) 50 ppm	Middle (10) 200 ppm	High (9) 800 ppm
WBC	8.3±2.4	7.4±1.5	8.4±2.1	6.6±2.5
RBC	7.3±0.4	7.6±0.6	7.7±0.5	7.4±0.5
HCT	43.3±2.3	45.0±2.5	45.7±2.8	45.6±2.8
HGB	14.2±0.6	14.6±0.6	14.7±0.9	14.6±0.7
MCV	59.2±2.9	59.1±2.0	59.7±2.8	60.4±2.1
MCH	19.5±0.9	19.2±0.8	19.3±0.9	19.3±0.7
MCHC	33.0±0.8	32.4±0.8	32.3±0.5*	32.0±0.8*
PLT	1118±230	1205±153	1492±129	1184±162

Numbers in parenthesis indicate the number of rats. * indicates significant difference at $p<0.05$ from those obtained in the control group. WBC, white blood cell counts ($10^3/mm^3$); RBC, red blood cell counts ($106/mm^3$); HGB, hemoglobin (g/dL); HCT, hematocrit (%); MCV, mean corpuscular volume (μ^3); MCH, mean corpuscular hemoglobin (pg); MCHC, mean corpuscular hemoglobin concentration (%); PLT, platelet counts ($10^3/\mu^3$).

Table 4. Hematology data of female rats treated with n-decane

	Control (10)	Low (10) 50 ppm	Middle (9) 200 ppm	High (10) 800 ppm
WBC	5.5±2.1	5.0±1.8	5.9±1.8	5.4±1.8
RBC	7.6±0.3	7.4±0.3	7.4±0.4	7.4±0.6
HCT	43.8±1.8	43.2±3.6	43.3±2.4	43.7±3.2
HGB	14.9±0.6	14.5±0.6	14.8±0.5	14.6±1.1
MCV	57.6±1.5	58.0±3.9	58.5±3.2	59.0±2.9
MCH	19.6±0.7	19.6±0.7	20.0±0.8	19.7±0.6
MCHC	34.0±0.7	33.8±1.8	34.2±1.6	33.4±1.4
PLT	1260±162	1286±164	1253±106	1052±373

Numbers in parenthesis indicate the number of rats. * indicates significant difference at $p<0.05$ from those obtained in the control group. WBC, white blood cell counts ($10^3/mm^3$); RBC, red blood cell counts ($106/mm^3$); HGB, hemoglobin (g/dL); HCT, hematocrit (%); MCV, mean corpuscular volume (μ^3); MCH, mean corpuscular hemoglobin (pg); MCHC, mean corpuscular hemoglobin concentration (%); PLT, platelet counts ($10^3/\mu^3$).

rease in the treatment group, but not a statistically significant level (Table 1 & 2).

3. Effects on hematology and blood biochemistry

A decrease in the number of white blood cells decreased in the high-dose male rats not statistically significantly (Table 3). The mean corpuscular hemoglobin concentration decreased in the middle- and high-dose male rats (Table 3). There were no significant changes of hematology values in the female rats (Table 4).

The blood chemical analysis of the n-decane-exposed male and female rats did not show any signi-

Table 5. Blood biochemistry data of male rats exposed to n-decane

	Control (10)	Low (10) 50 ppm	Middle (10) 200 ppm	High (10) 800 ppm
TP	6.9±0.3	6.8±0.2	6.9±0.2	7.0±0.3
BUN	11.7±0.8	12.4±1.8	11.3±1.1	13.4±2.8
CRTN	0.59±0.0	0.58±0.0	0.58±0.0	0.62±0.1
TBIL	0.12±0.0	0.13±0.1	0.10±0.0	0.12±0.0
GLU	138±12	129±8	131±10	146±20
TCHO	89±14	89±11	92±10	103±20
AST	159±52	142±25	36±27	149±32
ALT	40±12	33±9	30±8*	38±14

Numbers in parenthesis indicate the number of rats. * indicates significant difference at $p<0.05$ from those obtained in the control group. TP, total plasma protein (mg/dL); BUN, blood urea nitrogen (mg/dL); CRTN, creatinine (mg/dL); TBIL, total bilirubin (mg/dL); GLU, glucose (mg/dL); TCHO, total cholesterol (mmol/L); AST, aspartate aminotransferase (units/L); ALT, alanine aminotransferase (units/L); ALP, alkaline phosphatase (units/L).

Table 6. Blood biochemistry data of female rats exposed to n-decane

	Control (10)	Low (10) 50 ppm	Middle (10) 200 ppm	High (10) 800 ppm
TP	6.8±0.4	6.9±0.2	6.7±0.2	6.8±0.4
BUN	13.3±2.1	12.8±2.0	13.0±1.6	12.3±1.9
CRTN	0.62±0.0	0.60±0.0	0.61±0.0	0.59±0.0
TBIL	0.10±0.0	0.10±0.0	0.09±0.0	0.12±0.1
GLU	119±19	111±15	106±15	131±17
TCHO	95±17	108±19	96±18	109±17
AST	138±25	126±18	140±27	144±31
ALT	25±7	20±4*	21±5	31±13

Numbers in parenthesis indicate the number of rats. * indicates significant difference at $p<0.05$ from those obtained in the control group. TP, total plasma protein (mg/dL); BUN, blood urea nitrogen (mg/dL); CRTN, creatinine (mg/dL); TBIL, total bilirubin (mg/dL); GLU, glucose (mg/dL); TCHO, total cholesterol (mmol/L); AST, aspartate aminotransferase (units/L); ALT, alanine aminotransferase (units/L); ALP, alkaline phosphatase (units/L).

ficant increase in total protein, blood urea nitrogen, cratinine, total bilirubin, glucose, total cholesterol, aspartate aminotransferase or alanine amiotransferase (Table 5 & 6).

4. Histopathological examination

Histopatholgoical examination on the testes in the high-dose group showed extensive vacuolizations in the seminiferous tubules in several rats (Fig. 3B).

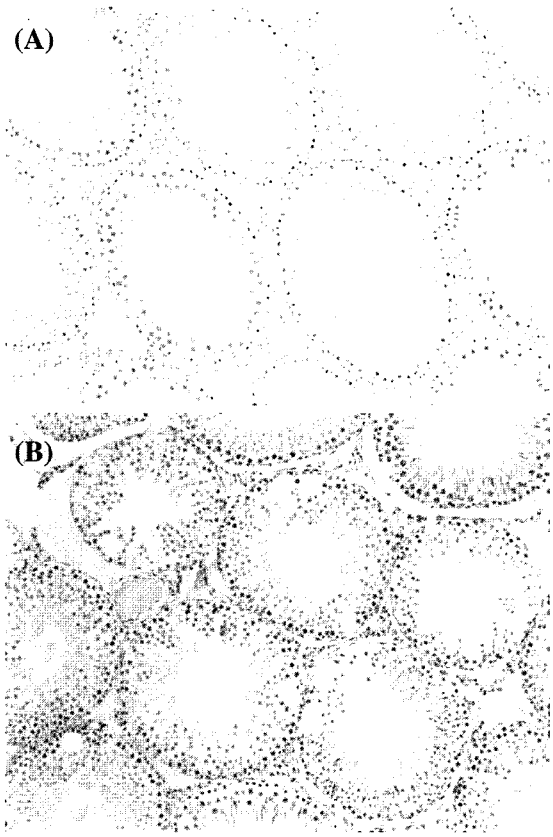

Fig. 3. Vaculoizations in the seminiferous tubules. (A) Control shows normal tubules with healthy looking germ cells; (B) n-decane at 800 ppm, extensive vacuolizations in the seminiferous tubules. Several tubules are atrophic. (200× objectives).

Comparing with the control group (Fig. 3A), atrophic tubules were also detected in the high-dose group (Fig. 3B). Other organs, such as the liver, kidneys, spleen, lungs, adrenals, heart and brain were examined histopathologically, with no distinct findings.

DISCUSSION

This study was conducted to investigate possible toxicity of n-decane when used in electronics industry as a cleaning solvent. The cleaning solvents we investigated were used without sufficient toxicological information. Although the electronic industry,

especially semiconductor industry, is one of the cleanest and regarded as rather safer industry, it could produce serious occupational diseases or injuries (Schenker, 1996; Chepesiuk, 1999). The electronic industry has been known to produce a high incidence of occupational illnesses. Toxic materials, metals, photo-active chemicals, solvents, acids, and toxic gases are used in a wide variety of combinations and workplace settings (Ladou and Rohm, 1998). An incidence of mass reproductive and hematopoietic intoxication of workers by exposure to cleaning solvent has been reported in the electronic industry (Kim *et al.*, 1996; Yu *et al.*, 1997). The workers from the electronics industry in Singapore experienced high incidence of skin disease due to exposure to common irritants, including nickel, resin, soldering flux, oils and coolants, solvents, acids and alkalis (Tan *et al.*, 1997). Despite finding no evidence of an increased risk of spontaneous abortion, the semiconductor industry has been investigated for this risk in female semiconductor workers (Elliott *et al.*, 1999). Although many chemicals in the electronic industry prepared or existed as mixtures, MSDS of chemicals in the industry did not provide sufficient information due to lack of toxicological data (Yun *et al.*, 2000; Welsh *et al.*, 2000). Many MSDS also did not have information on occupational exposure level and physico-chemical properties. The occupational exposure levels of Stoddard solvent or naphthas were difficult to apply workplace of electronic industry, because exposure monitoring and evaluation on mixture solvents were so complicated.

In this report, we have tried to provide toxicological information on n-decane, which is commonly found in mixture solvents, including isomeric forms. The toxicities of n-decane are very minimal in our 28-days of inhalation toxicity experiment. They showed minimal body weight changes and did not show any target organ toxicity. The blood biochemical and hematological data also did not show any significant toxicity.

We examined reproductive organ extensively because there were some degree of organ weight decreases in the reproductive organs of the male and female rats, although they were not statistically significant. The vacuolization of the seminiferous tubules of male testes in the high-dose group could be due to either stress caused by placing rats in wire cages or exposure related results during the 28-day of exposure period. We have evaluated the difference of vacuolization between exposure groups. Although most seminiferous tubules had a minimum degree of vacuolization due to histological fixation, stress, or unknown reasons, only three cases of extensive vacuolization with atrophy in the seminiferous tubules were observed at the high-dose group and three cases each in a less degree in the middle- and low-dose groups, respectively. Although our histopatholoigical evaluation on the testes showed some minimal dose-responses after 28 days of decane exposure, some more experiments or studies are needed to confirm the reproductive toxicity of decane. Thus, the meaning of this vacuolization could not be interpreted in this experiment.

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