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8EHQ-97-14093

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49980000195s

May 11, 1998

Mr. Ed Gross  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, DC 20460

Dear Mr. Gross:

Per our phone conversation, enclosed please find a resubmission of 8(e) report which was previously submitted on May 7. The appropriate CBI has been bracketed and sanitized.

Sincerely,

[Redacted signature area]

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May 11, 1998

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U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, DC 20460

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Attention: 8(e) Coordinator

Dear 8(e) Coordinator:

Re: Follow-up on 1-Propyl Bromide (CAS# 106-94-5)  
8(e) Submission of December 22, 1997

This letter is submitted in accordance with Section 8(e) of the Toxic Substances Control Act, 15 USC 2607(e), and the Environmental Protection Agency's "Statement of Interpretation and Enforcement Policy", 43 FR 1110, 35 seq., March 16, 1978.

On December 22, 1997, we submitted to the EPA 8(e) coordinator a conference handout of a Japanese study on 2-bromopropane and 1-bromopropane. It has come to our attention two additional 1-bromopropane (CAS# 106-94-5) papers were presented at another Japanese conference on April 20-24, 1998. One of the two was a follow up to our December 22, 1997 8(e) submission. We received the conference handouts in Japanese and we translated them internally. While this translation was prepared in good faith and is being used internally, the translator is not a professional scientific translator and therefore we cannot guarantee the accuracy of the translation. Enclosed as follows are the conference handouts and translations.

- Attachment 1. Manabu Ichihara Study Summary
- Attachment 2. Translation of Ichihara Summary
- Attachment 3. Baigyoku Oh Study Summary
- Attachment 4. Translation of Oh Summary

8(e) Coordinator  
May 11, 1998  
Page 4

As in the previous study, many details of the methodology are unknown. We do not know whether either of these Japanese studies has been submitted for publication.

If you have any questions, please contact me at [ ]].

Sincerely,

[ ]

[ ]

Attachments

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1-プロモプロバンの神経毒性

○市原学<sup>1</sup>、兪小忠<sup>1</sup>、柴田英治<sup>1</sup>、鬼頭純三<sup>2</sup>、朝枝伸幸<sup>3</sup>、謝振麟<sup>1</sup>、王海蘭<sup>1</sup>、竹内康浩<sup>1</sup> (1名古屋大医衛生、2名古屋大医動物実験施設、3三和化学安全性研究所)

[目的] 我々の先の実験において、1-プロモプロパン (1-BP) 1000ppm 曝露群の神経伝導速度が、2-プロモプロパン 1000ppm 曝露群のそれに比べて早い時期に低下した。我々は、1-BP の末梢神経に対する影響を明らかにするためにラットを用いた 12 週間濃度段階別吸入曝露実験を行った。併せて精子に対する影響も調べた。

[方法] 36 匹のウイスター系雄ラットを無作為に 4 群に分け、3 つの群に対して、それぞれ 800ppm、400ppm、200ppm の 1-BP 曝露を一日 8 時間、週 7 日、12 週間行った。対照群には新鮮空気のみを与えた。4 週毎に握力 (前脚、後脚)、尾の運動神経伝導速度 (MCV)、遠位潜時 (DL) を測定した。曝露開始 12 週間後に解剖し、精巣上体尾部重量あたりの精子数、運動精子率を血球計算盤を

用いて測定した。分散分析の後、対照群と各曝露群との比較を Dunnnett の多重比較によって行った。

[結果] 曝露濃度の実測値は 821±38、412±24、208±15ppm (Mean±SD) であった。四肢の握力は曝露を続けるに伴って量依存的に減少した (Fig. 1, 2)。DL、MCV は、800ppm で各々有意に増加、減少した (Fig. 3, 4)。精子数、運動精子は 400ppm 以上で有意に減少した (Fig. 5, 6)。200ppm では上記各指標の有意な変化は観察されなかった。

[結論] 握力、神経伝導速度、精子指標の量依存的な変化より、1-BP が末梢神経毒性をもち、精子数、精子の運動性を減少させることが明らかとなった。

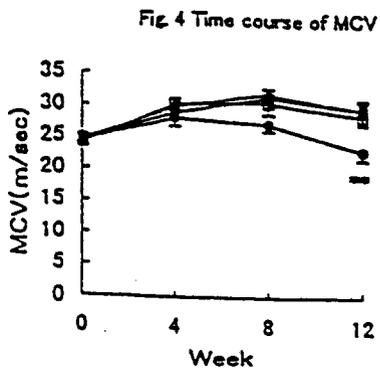
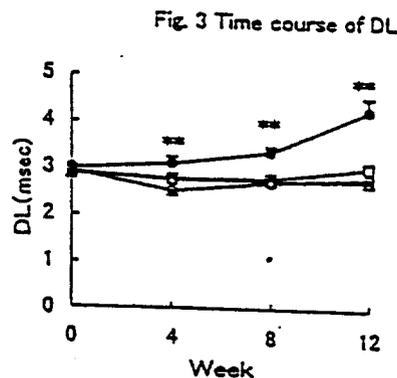
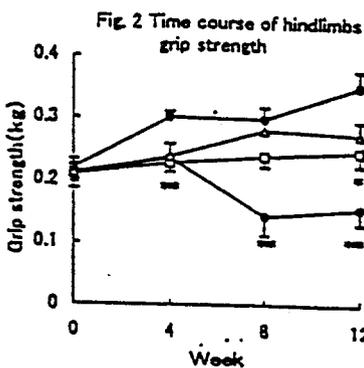
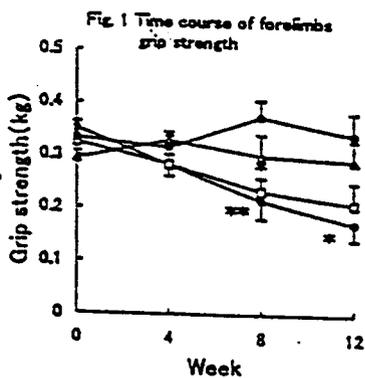


Fig. 5 Effects of 1-BP on sperm count

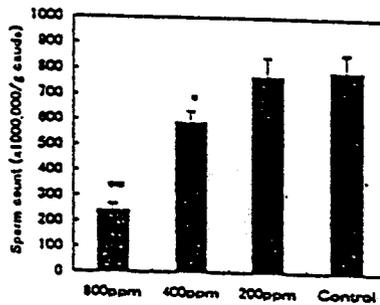
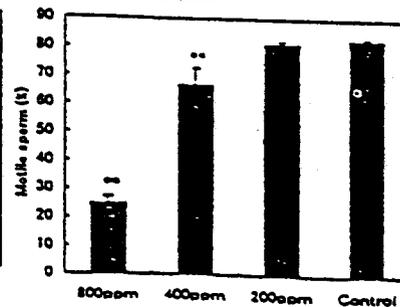


Fig. 6 Effects of 1-BP on percentage of motile sperm



○ Control, △ 200ppm 1-BP, □ 400ppm 1-BP, ● 800ppm 1-BP. Vertical lines depict SEM.  
\* p < 0.05, \*\* p < 0.01 (Significant in comparison with the control by Dunnnett's method)

# Neurotoxicity of 1-Bromopropane

Nagoya University, Medical School

Manabu ICHIHARA

Yasuhiro TAKEUCHI

Eiji SHIBATA

Junzo KITOH

3 Chinese researchers

Nobuyuki ASAEDA (Sanwa Chemical  
Safety Lab.)

## PURPOSE :

In our previous experiments, we found that the neurotransmittance velocity of the animal set that was exposed to 1000 ppm of 1-BP became depressed in shorter time than that of 1000 ppm 2-BP animal set did. In order to study the effect of 1-BP to peripheral nerve, we conducted 12 weeks inhalation exposure test on rat by exposure levels. Effects to sperm were also investigated.

## METHOD :

36 male Wister rats were randomly segregated into 4 groups. 3 groups were respectively exposed to 800 ppm, 400 ppm and 200 ppm of 1-BP for 8 hours a day, 7 days a week for 12 weeks. Control group was exposed only to fresh air. At the end of each 4 weeks, grip strength of forelimbs and hindlimbs, MCV of tail and DL were measured. Rats were sacrificed 12 weeks after the start of exposure, and the count of sperm per weight of spermary end and the rate of moving sperm were measured using a blood count spectrum. After the dispersed analysis, control group and exposed groups were compared by Dunnett multi comparison method.

## RESULT :

Actual exposure levels were determined as  $821 \pm 38$ ,  $412 \pm 24$  and  $208 \pm 15$  ppm (Mean  $\pm$ SD). Grip strength of fore and hind limbs decreased volume-dependently as exposure continued (Fig. 1,2). DL and MCV increased or decreased meaningfully in 800 ppm (Fig. 3,4). Count of sperm and moving sperm decreased meaningfully in 400 ppm or above (Fig. 5,6). No changes of those indications were observed in 200 ppm.

## CONCLUSION :

From the observations of volume-dependent changes in grip strength, neurotransmittance velocity and sperm indications, it was revealed that 1-BP has peripheral nerve toxicity and decreases count of sperm and movability of sperm.

1302

1-bromopropane がマウス脳内  $\beta$ -amyloid protein の translation におよぼす影響 —若年マウスと成年マウスの比較

○王 培玉, 金子 蒼, 佐藤章夫  
山梨医大・第一保健

【目的】近年、2-bromopropane と 1-bromopropane (1-BP) の生殖、骨髄、神経毒性が注目を集めているが、老化におよぼす影響については報告が少ない。今回、私達は、1-BP をマウス (若年と成年) に投与し、Northern blot を用いて老化の biomarker の一つである脳内の  $\beta$ -amyloid protein におよぼす影響を mRNA レベルで測定したので報告する。

【方法】若年 (6 週齢) および成年 (8 ヶ月齢) の雄性 ICR マウスをそれぞれに对照群と 1-BP 投与群に分けた。对照群に corn oil、投与群に 1-BP (0.27 g/kg, corn oil 溶液として 4.0 ml/kg) を 5 日間連続、腹腔内投与した。最終投与の翌日午前 10 時に、動物を屠殺し脳組織を採取、ISOGEN kit (ニッポンジーン社) を用いて RNA を抽出し、Northern blot analysis を行った。 $\beta$ -amyloid protein の mRNA のプローブは oligonucleotide (シークエンス: 5-CCG TCG TGG GAA CTC GGA CTA CCT-3) を用いた。プローブを Dig Tailing kit (ペーリンガー社) でラベルした。total RNA はアガロース変性ゲルを用いた電気泳動で分離し、RNA を nylon-membrane へ転写し、ハイブリダイゼーションを行った。その後、目的の mRNA を乗せた nylon-membrane を Dig Luminescent Detection kit (ペーリンガー社) で検出処理し、X-ray film に暴露した。検出した mRNA のバンドを densitometer で数値化した。

【結果と考察】成年マウスは若年マウスと比べ、 $\beta$ -amyloid protein の mRNA が有意に高かった (Table)。若年マウスでは对照群と投与群の間に有意差は見られなかったが、成年マウスでは 1-BP 投与群において  $\beta$ -amyloid protein の mRNA が对照群より有意に上昇した (Table)。 $\beta$ -amyloid protein はもともと Alzheimer's disease 患者の脳組織に多量存在するものであり、近年、老化の biomarker の一つとして注目を集めている。本研究で 1-BP が成年

マウスの  $\beta$ -amyloid protein の mRNA を増加させたことは、1-BP が生体の老化を促進する可能性を示唆している。

【謝辞】本研究は、上海医科大学労働衛生学教室の賈曉東博士との共同で行った。

Table. Arbitrary density units of mRNA in brain of mice

Group	Young	Adult
Control	0.64±16	0.90±0.16*
1-BP	0.66±14	1.18±0.20**

\*Significantly different from Young mice ( $p < 0.05$ ,  $n = 5$ ).  
\*\*Significantly different from Control.

# Effects of 1-BP to the Translation of Beta-amyloid protein in Mouse Brain Comparison between Young Mouse and Adult Mouse

Yamanashi Medical College  
No.1 Hygiene Dept.

Baigyoku OH  
Homare KANEKO  
Akio SATO

## PURPOSE :

2-Bromopropane and 1-Bromopropane are watched recently for reproductive, bone marrow and neuro toxicities, however no report was seen for those effect to ~~senility~~ aging. We gave 1-BP to young and adult mice and measured those effects to beta-amyloid protein in the brain, one of the biomarkers for ~~senility~~ aging, using Northern blot in mRNA level.

*senility*

## METHOD :

Young (6 weeks) and adult (8 months) male ICR mice were respectively segregated into control groups and 1-BP feeding groups. Control groups were fed of corn oil, and 1-BP groups were fed of 0.27 g/kg of 1-BP or 4.0 ml/kg as corn oil solution, for 5 days continuously into abdominal cavity. At 10:00 a.m. of the following day of the last feeding, animals were sacrificed and brain tissues were obtained. RNA was extracted from the brain using ISOGEN kit and Northern blot analysis was done. Oligonucleotide (sequence : 5-CCG TCG TGG GAA CTC GGA CTA CCT-3) was used for mRNA probe of beta-amyloid protein. The probe was labeled with Dig Tailing kit. Total RNA was separated by electrical swimming using agarose modified gel, and RNA was transcribed to nylon-membrane and hybridization was given. The targeted mRNA was detected from nylon-membrane through Dig Luminescent Detection kit and exposed to X-ray film. Detected mRNA band was numericalized by densitometer.

## RESULT and FINDING :

mRNA of beta-amyloid protein was meaningfully higher in adult mice compared to that of young mice (table). Although there was no difference of mRNA between the control group and 1-BP group of young mice, it was meaningfully increased in the 1-BP group of adult mice (table). Beta-amyloid protein exists in the brain tissue of Alzheimer's disease patients to large extents and it is watched recently as a biomarker of ~~senility~~ aging. 1-BP increased mRNA of beta-amyloid protein of adult mice in this study, which implies that 1-BP has a potential of increasing ~~senility~~ aging.

*senility*

7/15/99

**Ethylidenenorbornene (ENB)**

The study was designed to investigate the mechanism of action of ENB on the thyroid and to establish a NOEL. ENB was given by gavage in corn oil to groups of 10 male CD rats at dose levels of 0, 50, 200 or 350 mg/kg/day, or at 0, 50, 200 or 300 mg/kg/day for 14 days. A negative control group, receiving corn oil only, and a positive control group, receiving 3 mg/kg/day of Propylthiouracil (PTU), were included. ENB at relatively high doses of 250, 300 or 350 mg/kg/day, produces a mild hyperactive response in the thyroid, characterized by hyperplasia and by an increase in small acini and tall columnar cells. Dose of 50 mg/kg/day caused no effect and is considered as a NOEL. The statistically significant increase in the liver/body weight ratio, and the slight but biologically significant increase in microsomal activity would suggest the response of the thyroid is mediated by the liver/thyroid axis. The thyroid effect of ENB is considered of moderate concern

**1-Bromopropane (1-BP)**

JEHQ-0598-14093 S Supp

The original report was presented at a Japanese conference on April 20-24, 1998. A Japanese handout and an English translation was submitted. 1-BP was administered by inhalation to groups of 9 male Wistar rats at dose levels of 0, 208, 412, or 821 ppm, 8 hours a day, 7 days a week, for 12 weeks. The control group was exposed only to fresh air. Exposure of 1-BP resulted in peripheral nerve toxicity as evidenced by decreases in grip strength of fore and hind limbs; increases or decreases in DL (not translated) and MCV (not translated) of the tail; and caused decreases in count of sperm and movability of sperm. No effects were observed at 208 mg/kg/day. Based on the dosage employed in the study, the toxicity of 1-BP is considered of moderate concern

EPA  
Evaluation  
Section  
V.8

**Dimethyldichlorosilane, reaction products with silica**

The acute inhalation toxicity of the test substance is of moderate concern. The test substance was tested in 5 male and 5 female rats in aerosol atmosphere at dose levels of 0.21, 0.54 or 2.1 mg/L in accordance with EPA guideline (Subdivision F, Series 81-3, TSCA 40 CFR 798.1150). A 4-hour LC50 of 0.45 mg/L was calculated

**Dicyclohexylmethane 4,4'-diisocyanate (Desmodur W)**

The acute inhalation toxicity of Desmodur W is of moderate concern. The test substance was tested in male and female Wistar rats in aerosol atmosphere in accordance with OECD guideline No. 403. A 4-hour LC50 of 456 or 431 mg/m<sup>3</sup> was calculated for males or females, respectively. Toxic signs consisted of irritation to the respiratory tract and damage to the lungs including hemorrhagic edema which was regarded as the cause of death. There were no indications of delayed-onset of toxicity.