February 7, 2017

Catherine McCabe
Acting Administrator
Environmental Protection Agency Office of Administrator (1101A)
1200 Pennsylvania Avenue, NW
Washington, D. C. 20460

Mr. Steve Page
U.S. EPA, Office of Air Quality Planning and Standards
Sector Policies and Programs Division
Policies and Strategies Group, Mail Code D205-02
Research Triangle Park, North Carolina 27711

Subject: **ICL's Request to comment on nPB petition EPA Docket ID No. EPA-HQ-OAR-2014-0471 –** Draft notice for granting petitions to add n-Propyl Bromide to the List of Hazardous Air Pollutants, Docket ID No. EPAHQ-OAR-2014-0471

Dear Ms. McCabe & Mr. Page,
The Environmental Protection Agency (EPA) is publishing a draft notice of the rationale for granting petitions to add n-propyl bromide (nPB), also known as 1-bromopropane (1-BP), (Chemical Abstract Service No. 106-94-5) to the list of hazardous air pollutants (HAP) contained in section 112(b)(1) of the Clean Air Act (CAA).

According to the docket, EPA states they have determined there is adequate evidence to support a determination that emissions and ambient concentrations of nPB may reasonably be anticipated to cause adverse health effects.

ICL would like the agency to reconsider this decision in view of new health effect data ICL has recently obtained to support n-Propyl bromide REACH registration. A copy of this study summary is attached in this response. The title of the study is identified below:

> ***In Vivo* Mutation Assay of n-Propyl Bromide at the *cII* Locus in Big Blue® Transgenic B6C3F1 Mice Exposed via Whole-Body**

ICL submitted a copy of the full report to EPA for the consideration of the TSCA Work Plan Chemical Risk Assessment Review for 1-bromopropane (n-propyl bromide).

As you can see from the study summary, the treatment with n-propyl bromide did not cause statistically elevated mutant frequencies at the *cII* gene in liver and lungs of Big Blue® female mice. The positive control treatment with ENU produced statistically significant increases in mutant frequencies for both tissues tested, demonstrating the utility of the test system to detect and quantify induced mutants following exposure to a known direct acting mutagen. The study design and results obtained met protocol-specified assay acceptance

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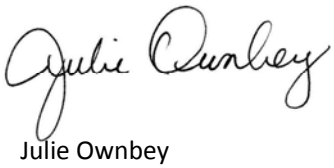
criteria and were consistent with the study requirements of OECD TG 488 for transgenic rodent mutation assays, supporting the conclusion that n-propyl bromide is negative for the induction of *cII* mutants in liver and lungs of Big Blue® female mice under the conditions of testing.

Therefore it can be concluded that the carcinogenic pathway of this substance is not genotoxic, and that it depends on exposure threshold.

We would also like to emphasize that, n-propyl bromide should not pose negative health impact in controlled environment, and therefore further restriction regulatory measures for this substance, such as adding it under HAP are not justified.

Please feel free to contact me if you have any questions regarding this letter or the summary at 304-675-1150.

Sincerely,



Julie Ownbey
Regulatory Affairs Manager

Attached: study summary for *In Vivo* Mutation Assay of n-Propyl Bromide at the *cII* Locus in Big Blue® Transgenic B6C3F1 Mice Exposed via Whole-Body Inhalation.

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In Vivo Mutation Assay of n-Propyl Bromide at the *cII* Locus in Big Blue® Transgenic B6C3F1 Mice Exposed via Whole-Body Inhalation

FINAL REPORT

Test Substance

n-Propyl Bromide

Author

Robert R. Young, M.S.

Study Completion Date

09 September 2016

Testing Facility

BioReliance Corporation (BioReliance)
9610 Medical Center Drive
Rockville, MD 20850

BioReliance Study Number

AE49SJ.170.BTL

Sponsor

ICL-IP
P.O. Box 180
Beer-Sheva, 84101 Israel

Sponsor Representative

Dr. Orit Manor

1. SUMMARY

The purpose of this study was to determine the effect of the test substance, n-propyl bromide (also known as 1-bromopropane), on mutant frequency at the *cII* gene in liver and lung from female transgenic Big Blue® B6C3F1 mice following whole-body inhalation exposure for 6 hours per day on a 7 day per week basis for 4 weeks (28 exposures for each animal). The Big Blue® Assay is a Transgenic Rodent (TGR) mutation assay, described in OECD Test Guideline (TG) 488 (OECD, 2013).

The in-life and post-mortem portions of the study were conducted at WIL Research. The Big Blue® mutation assay portion of the study was conducted at BioReliance Corporation. Due to the acquisition of WIL Research by Charles River, the name of the WIL Research facility in Ashland, OH has been changed to Charles River Laboratories Ashland, LLC, 1407 George Road, Ashland, OH 44805, USA. Study documents may contain both names and both names are considered equivalent and may be used as the name WIL Research transitions to Charles River.

The test substance, n-propyl bromide, was administered via whole-body inhalation exposure for 6 hours per day for 28 consecutive days to 3 groups (Groups 2, 3 and 4) of female Big Blue® B6C3F1 mice. Target exposure concentrations were 62.5, 125 and 250 ppm for Groups 2, 3 and 4, respectively. A concurrent control group (Group 1) was exposed to humidified, filtered air on a comparable regimen. Each group consisted of 6 female animals. The first day of exposure for this study report was designated as Day 1. On Day 31, the third day after the last dose administration, all animals were euthanized. The first day of inhalation exposure is defined by the Test Site (WIL Research) as Day 0, while the Testing Facility (BioReliance) defines the first day of exposure as Day 1.

All animals were observed twice daily for mortality and moribundity. Clinical examinations were performed twice daily on the days of exposure, prior to exposure and at 0-1 hour (+ 0.25 hour) [presented as 1 hour post-exposure for report presentation purposes] following exposure, and once daily on non-exposure days. Detailed physical examinations were performed and individual body weights (non-fasted) were recorded within 4 days of receipt, on the day of randomization, weekly (± 1 day) during the study period, and on the day of the scheduled necropsy. Individual food weights were recorded once weekly (± 2 days) beginning after randomization and throughout the study period, including the day of the scheduled necropsy. In order to minimize the *in situ* degradation of the DNA, all animals were euthanized by carbon dioxide inhalation, and the liver and lungs were weighed (for prediction of the number of DNA extractions possible from a tissue), flash frozen in liquid nitrogen, and stored at approximately -80°C. The tissues were shipped on dry ice via overnight courier to BioReliance, Rockville, MD, for *cII* mutant analysis.

As specified in the study protocol, the liver and lungs from 5 animals per group were processed for DNA isolation and analysis of *cII* mutants, following BioReliance SOP's. Due to the elevated mutant frequency in lung DNA from one animal in both Groups 2 and 3, the sixth animal in each of these groups was also extracted and analyzed for *cII* mutants.

In addition, liver and lung tissue samples were processed for DNA isolation from frozen tissues from 5 positive control-treated animals, collected as part of BioReliance Corporation Study Number AE34AA.170.BTL. This positive control group is identified in post-life data as Group 5. This use of "packaging controls" is permitted by OECD TG 488. The goal of the positive control group was to demonstrate the ability to recover induced mutants from the study target tissues. Positive control tissues from target organs were collected on Testing Facility Study Day 31 after the start of dosing (Day 1 was defined by Testing Facility as the first day of dosing) from Big Blue® B6C3F1 female mice exposed by oral gavage to 40 mg/kg/dose of ethyl nitrosourea (ENU) on Study Days 1, 2 and 3. ENU is a potent direct acting mutagen, demonstrated to be mutagenic in the target tissues.

The study was designed to investigate the possibility for a mutagenic mode of action for tumor formation, primarily in the lungs, at the request of ECHA (European Chemicals Agency) under the REACH Regulation. The target exposure concentrations and the exposure regimen (6 hours/day for 7 days/week for a 28-day period) were selected by the Sponsor's Representative and are consistent with those recommended in OECD Test Guideline 488 (OECD, 2013). Since the request for the TGR assay was based on the National Toxicology Program (NTP) carcinogenicity study in B6C3F1 mice (NTP, 2013), tumorigenic dose levels (ranging from 62.5 to 250 ppm) and exposure conditions (inhalation) were established to match those of the NTP study design. The only modification was the use of a 6 hour/day, 7 day/week dosing regimen for 28 days. The modification of exposure for 7 days per week was used to be compliant with the OECD TG 488 which specifies a 7 day/week exposure for 28 days, which represented the worst case. The design is sufficient to permit genetic damage and fixation of the damage into detectable mutants if n-propyl bromide carcinogenicity is due to a mutagenic mode of action.

Treatment with n-propyl bromide did not cause statistically elevated mutant frequencies at the *cII* gene in liver and lungs of Big Blue® female mice. The positive control treatment with ENU produced statistically significant increases in mutant frequencies for both tissues tested, demonstrating the utility of the test system to detect and quantify induced mutants following exposure to a known direct acting mutagen. The study design and results obtained met protocol-specified assay acceptance criteria and were consistent with the study requirements of OECD TG 488 for transgenic rodent mutation assays, supporting the conclusion that n-propyl bromide is negative for the induction of *cII* mutants in liver and lungs of Big Blue® female mice under the conditions of testing. Therefore, n-propyl bromide is considered not mutagenic in the mouse transgenic rodent mutation assay.