FINAL REPORT

Immunotoxicological Evaluation of Baseline Gasoline Vapor Condensate Using the Plaque-Forming Cell Assay

Test Substance: Baseline Gasoline Vapor Condensate

Protocol No: HLS 00-6125

Subcontractor's Sponsor: Huntingdon Life Sciences
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ImmunoTox's Project Number: ITI 900

Date: 01 April 2005

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I. STATEMENT OF COMPLIANCE

This study was conducted in compliance with the United States Environmental Protection Agency’s (EPA) Good Laboratory Practice Standards 79.60, CFR Vol. 59, No. 122, 27 June 1994 with the following exceptions:

1. It was the Sponsor’s responsibility to maintain the methods of synthesis, fabrication, or derivation of the test fuel. This had not been completed when the study initiated but is currently with the Sponsor.

2. The identity, strength, purity and composition or other characteristics to define the positive control article have not been determined by the Testing Facility. The positive control article has not been characterized as per the Certificate of analysis on file with the Testing Facility. The stability of the positive control article has not been determined by the Testing Facility. Analyses to determine the uniformity (as applicable) or concentration of the positive control mixture were not performed by the Testing Facility. The stability of the positive control article mixture has not been determined by the Testing Facility.

Gary M. Hoffman, B.A., D.A.B.T.
Study Director

Date

Thomas M. Gray, M.S., D.A.B.T.
Sponsor Representative

Date
II. QUALITY ASSURANCE STATEMENT – IMMUNOTOX

Test Substance: Baseline Gasoline Vapor Condensate

Report Title: Immunotoxicological Evaluation of Baseline Gasoline Vapor Condensate Using the Plaque-Forming Cell Assay

Protocol Title: Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats with Neurotoxicity Assessments and 4-Week in vivo Genotoxicity and Immunotoxicity Assessments

Huntingdon Life Sciences, Inc. Study No. 00-6125
Sponsor Study No. 211-B-S

The final report for the indicated protocol has been reviewed by the Quality Assurance Unit of Virginia Commonwealth University. Furthermore, the Quality Assurance Unit has conducted the following inspections and reported to the ImmunoTox, Inc. Principal Investigator, and then has submitted written reports of said inspections to the Study Director and Management via the Principal Investigator.

Inspection/Audits were performed and reported on the following dates:

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Approved and submitted by: [Signature] Quality Assurance Manager

Date: 01 April 05
QUALITY ASSURANCE STATEMENT - HUNTINGDON

Listed below are the dates that this study was inspected by the Quality Assurance Unit of Huntingdon Life Sciences, East Millstone, New Jersey, and the dates that findings were reported to the Study Director and Management. This report reflects the raw data as far as can be reasonably established.

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Fran Jannone, B.A., RQAP-GLP
Quality Assurance Group Leader
III. SIGNATURE OF PRINCIPALS

This report describes the results used to evaluate the relative immunotoxicological potential of the test substance, Baseline Gasoline Vapor Condensate, which was administered by inhalation via whole-body exposure to female Sprague Dawley rats.

Kimber L. White, Jr., Ph.D., Principal Investigator, was responsible for the overall conduct of the immunotoxicity evaluations in this study. Vanessa L. Peachee, M.S., served as the Assistant Principal Investigator and was responsible for the day-to-day activities of the immunotoxicity evaluations in this study.

Kimber L. White, Jr., Ph.D.  
Principal Investigator  
ImmunoTox, Inc.

Vanessa L. Peachee, M.S.  
Assistant Principal Investigator  
ImmunoTox, Inc.

Approved:

Gary M. Hoffman, B.A., DABT  
Study Director  
Huntingdon Life Sciences
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APPENDICES

A Individual Animal Data

B Contracting Sponsor's Exposure and Animal Data
IV. EXECUTIVE SUMMARY

The study was conducted as part of Huntingdon Life Sciences (HLS) Study No. 00-6125 at ImmunoTox, Inc., Richmond, Virginia. The Principal Investigator was Kimber L. White, Jr., Ph.D., and Vanessa L. Peachee, M.S., served as the Assistant Principal Investigator. The study was conducted to provide evaluation of immunological parameters for Huntingdon Life Sciences.

The objective of the study was to determine the potential effects of Baseline Gasoline Vapor Condensate for its ability to affect the humoral immune component of the immune system, when evaluated in the antibody-forming cell response to the T-dependent antigen sheep erythrocytes. Female Sprague Dawley rats were administered Baseline Gasoline Vapor Condensate for 5 days per week for 4 weeks by inhalation via whole body exposure by Huntingdon Life Sciences (HLS) Princeton Research Center (PRC) personnel. Three exposure levels of 2000, 10000 and 20000 mg/m³ of the test substance were used in the study. The in-life phase of the study was conducted by HLS, East Millstone, NJ, and the immunological evaluation was conducted by ImmunoTox, Inc., Richmond, VA. On the day of sacrifice, spleens were placed in tubes containing media, placed on ice pack, and shipped to ImmunoTox, Inc. in Richmond, VA, for assay evaluation on the following day.

Executive Summary Table ES-1 shows a summary of the selected toxicology and immunology parameters evaluated. Exposure resulted in no statistically significant changes in body weight for any exposure level. There were no statistically significant effects observed in either thymus or spleen weight following exposure to Baseline Gasoline Vapor Condensate, when evaluated as either absolute or relative weight (% body weight), as compared to the air control.

Exposure to Baseline Gasoline Vapor Condensate did not result in significant changes in the IgM antibody-forming cell (AFC) response to the T-dependent antigen, sheep erythrocytes, when evaluated as either specific activity (AFC/10⁶ spleen cells) or as total spleen activity (AFC/spleen).

In conclusion, the results of this immunotoxicological evaluation demonstrate that, under the experimental conditions used, exposure to the Baseline Gasoline Vapor Condensate test substance did not adversely affect the functional ability of the humoral immune component of the immune system.
Table ES-1

SUMMARY TABLE FOR TOXICOLOGY AND IMMUNOLOGY STUDIES

<table>
<thead>
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<th>Parameter</th>
<th>Result</th>
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<th>Dose</th>
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</tr>
<tr>
<td>Day 29</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Organ Weights</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>No Effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymus</td>
<td>No Effect</td>
<td></td>
<td></td>
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<td><strong>Spleen IgM Antibody-Forming Cell Response to Sheep Erythrocytes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IgM AFC to sRBC</td>
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The purpose of this study was to provide evaluation of immunological parameters for Huntingdon Life Sciences (HLS) Study No. 00-6125. In this study, the test substance, Baseline Gasoline Vapor Condensate, was evaluated for its ability to affect the humoral immune component of the immune system, when evaluated in the antibody-forming cell response to the T-dependent antigen sheep erythrocytes. The study was conducted in female animals because female rats have a more robust immune response than do the male animal of the species. Accordingly, female rats have a greater sensitivity for detecting an adverse effect of a compound should one occur. Routinely, immunotoxicology evaluations conducted by the National Toxicology Program (NTP) evaluate compounds only in female animals. Four days prior to sacrifice, ImmunoTox personnel sensitized the rats by intravenous administration of sheep erythrocytes at the HLS facility. On the day of sacrifice, HLS Princeton Research Center (PRC) personnel aseptically removed the spleen from each animal. The spleens were weighed, placed in tubes containing media, and sent to ImmunoTox, Inc. in Richmond, VA, on ice pack for evaluation the following day. Spleens were received on 10 January 2001 and the immunological evaluation was conducted on the same day. The IgM antibody-forming cell (AFC) response to the T-dependent antigen sheep erythrocytes, also referred to as the plaque assay, was the immunological assay conducted to evaluate the effect of Baseline Gasoline Vapor Condensate on the immune response. This assay has been shown to be the most predictive assay for determining the immunotoxicological potential of a compound (Luster et al.1).

Kimber L. White, Jr., Ph.D., was the Principal Investigator for the immunological evaluation conducted by ImmunoTox, Inc., and Gary M. Hoffman, B.A., D.A.B.T., was the HLS Study Director. Vanessa L. Peachee, M.S., served as the Assistant Principal Investigator for ImmunoTox, Inc. and was responsible for carrying out the IgM antibody-forming cell assay.

In evaluating the effects of Baseline Gasoline Vapor Condensate on the immune system, the immunologic and toxicologic parameters evaluated were: spleen and thymus weights, and the spleen IgM antibody response to the T-dependent antigen (sheep erythrocytes, sRBC).

To the best of our knowledge, no significant protocol or standard operating procedure deviations occurred during the study, which affected the quality of the data and the ability to interpret the data with respect to the immunotoxicology of Baseline Gasoline Vapor Condensate.
VI. METHODS OF PROCEDURE

EXPERIMENTAL DESIGN

The immunotoxicological satellite study consisted of a vehicle group, three exposure levels of Baseline Gasoline Vapor Condensate, and a positive control group. There were 10 female Sprague Dawley rats in each of the groups. Animals were exposed by Huntingdon Life Sciences Princeton Research Center (PRC) personnel to either vehicle (air only) or Baseline Gasoline Vapor Condensate at exposure levels of 2000, 10000 or 20000 mg/m³ via inhalation for 4 weeks (5 days per week). Cyclophosphamide (CPS) was given as the positive control. Cyclophosphamide (CAS #6055-19-2, Lot No. 108H0568, received 21 September 1999, expiration 30 June 2002, white powder, storage 2-8°C, purity 99.2%), was obtained from the Sigma Chemical Company (responsible for its characterization), and was dissolved and diluted in phosphate buffered saline at Huntingdon Life Sciences to stock concentrations of 5.0 mg/mL for use as the positive control for this study. The positive control animals received 50 mg/kg @ 10 mL/kg of CPS, a known immunosuppressive agent, administered intraperitoneally (i.p.) on the last 4 days of exposure. These animals were not chamber exposed. On the day of sacrifice, one day after the last exposure, PRC personnel aseptically removed the spleen from each animal, weighed it, placed it in a collecting tube containing Earle's Balanced Salt Solution (EBSS) with HEPES and Gentamicin solution (prepared at PRC), and shipped the spleens on ice in individual shipping containers at 2-8°C by carrier to ImmunoTox for overnight delivery. Upon receipt, spleens were further processed for determination of IgM antibody response.

VARIABLES ASSESSED

Terminal Body and Organ Weights. The terminal body weights were obtained by Huntingdon Life Sciences PRC personnel. Huntingdon Life Sciences PRC personnel collected blood (serum) samples (orbital collection anesthetized via carbon dioxide/oxygen inhalation) and then sacrificed (carbon dioxide inhalation) the animals on the day after the final exposure. The serum samples were frozen (-70°C). The thymuses were removed, weighed and preserved (formalin) for possible histopathology. Spleens were removed, weighed, and shipped at the time of sacrifice by PRC personnel to ImmunoTox, Inc. for immunotoxicological evaluation.

Splenic Oyt Preparation. Upon arrival at the ImmunoTox testing facility, spleens were accessioned in accordance with the SOP for receipt of biological samples. Single-cell suspensions
were prepared from each spleen using a Stomacher® 80 Lab Blender in accordance with the SOP for rat spleens. Cell suspensions were then centrifuged and resuspended in Earle's Balanced Salt Solution with HEPES. Viability of splenocytes were determined using propidium iodide (PI) and the Coulter EPICS XL-MCL Flow Cytometer.

**Spleen IgM Antibody Response to the T-dependent Antigen, sRBC. Day 4 Response.** As background, sheep erythrocytes (sRBC) are a T-dependent antigen and, thus, T cells, B cells, and macrophages are required to function properly in order to obtain an antibody-forming cell (AFC) response. If the test article affects any of these cell types to a significant degree, an altered response will be observed. As a result, the T-dependent IgM response to sRBC is one of the most sensitive immunotoxicological assays currently in use. A significant modulation in the IgM AFC response, when appropriately compared to vehicle controls, indicates that the test agent is capable of modifying the humoral immune response in the whole animal and, thus, has the potential for immunotoxicity. The plaque assay is regarded as the “Gold Standard” for evaluating effects of compounds on humoral immunity. Although the plaque assay is not considered to be an assay for cell-mediated immunity, since the assay utilizes a T-dependent antigen, it does provide limited information on T-helper cells and macrophages. As indicated above, if these cells are adversely affected, then an effect on humoral immunity can be detected with this assay. This assay is one of the Tier I assays used by the NTP.

The primary IgM response to sheep erythrocytes was measured using a modified hemolytic plaque assay of Jerne. Rats were exposed to the test article for 5 days per week for 4 weeks. Rats were sensitized by ImmunoTox, Inc. personnel with 2×10^8 sRBC i.v. four days prior to sacrifice and, on the day after the last exposure, animals were sacrificed by PRC personnel. Spleen cell suspensions were prepared as described above. The cells were centrifuged and resuspended in a 6-ml volume, and 1:50 and 1:150 dilutions were prepared. An 0.1-ml aliquot of spleen cells from each suspension was added to separate test tubes, each containing 25 μl guinea pig complement, 25 μl sRBC, and 0.5 ml of warm agar (0.5%). After thoroughly mixing, each test tube mixture was plated onto a separate petri dish, covered with a microscope cover slip, and incubated at approximately 36-38°C for 3 hours. One dilution per animal was evaluated. Spleen cell number, following lysis of RBC, was performed on the 6-ml samples using a Model Z1 Coulter Counter. The spleen weight, cells/spleen, AFC/10^6 spleen cells, and AFC/spleen were determined. The plaques that developed were counted using a Bellco plaque viewer. For each spleen, 2 dilutions (1:50 and 1:150) were prepared. At the time of counting, each plate was examined. Routinely, the plate that had between 100-300 plaques was counted. When the
number of plaques is in excess of 350 plaques per plate, it becomes difficult to obtain an accurate count using the Bellco viewer. A plaque, occurring from the lysis of sRBC, is elicited as a result of the interaction of complement and antibodies (produced in response to the i.v. sensitization) directed against sRBC. Each plaque is generated from a single IgM antibody-producing B cell, permitting the number of AFC present in the whole spleen to be calculated. The data are expressed as specific activity (AFC/10^6 spleen cells) and total spleen activity (AFC/spleen).

DATA

Data Handling and Statistical Analysis. The data obtained in this study were analyzed in accordance with standard operating procedure (SOP/CSA/006). Data were first tested for homogeneity of variances using the Bartlett's Chi Square Test. Homogeneous data were evaluated by a parametric one-way analysis of variance. When significant differences occur, exposed groups were compared to the vehicle control group using the Dunnett's t Test. Non-homogeneous data were evaluated using a non-parametric analysis of variance. When significant differences occur, exposed groups were compared to vehicle control group using the Gehan-Wilcoxon Test when appropriate. The Jonckheere's Test was used to test for exposure level-related trends across the vehicle and exposed groups. The positive control was compared to the vehicle control group using the Student t Test. The criteria for accepting the results of the positive control in the assay was a statistically significant (p ≤ 0.05) decrease in the response as compared to the vehicle control group.

P values of 0.05 or less, as compared to the vehicle control group, were considered statistically significant and are indicated in the tables and in the figures with a single asterisk (*). A double asterisk (**) was used to indicate a p value of 0.01 or less. In the text, the word significant indicates that the response was statistically significant at p ≤ 0.05. In the tables, the abbreviation NS is used to indicate *Not Significant* for p values greater than 0.05.

Data Retention. All data and records were returned to the Contracting Sponsor following acceptance of the final report. Records maintained for this protocol include: study sheet, chemical preparation form, and authorized signatures and initials forms. Upon completion of this study, the report and raw data for this study will be maintained in the archives of Huntingdon Life Sciences.
VII. RESULTS

TERMINAL BODY AND ORGAN WEIGHTS

The terminal body weight data from the study are shown in Table 1 for the control and Test Substance-exposed groups. No statistically significant effect was observed on terminal body weights of Baseline Gasoline Vapor Condensate-exposed rats as compared to the vehicle controls.

The organ weights of the control and Test Substance-exposed rats are shown in Table 1. No effect was observed, following exposure to Baseline Gasoline Vapor Condensate, on spleen or thymus weight when evaluated either as absolute or relative weight. Treatment with the positive control, cyclophosphamide, had a significant decrease of 57% on absolute spleen weight and a significant decrease of 75% on absolute thymus weight, compared to the vehicle control. In addition, the positive control, cyclophosphamide, had a significant decrease of 52% on relative spleen weight and a 72% decrease on relative thymus weight, compared to the vehicle control. Shown graphically in Figures 1 and 2 is the lack of effect on spleen and thymus weights following exposure to Baseline Gasoline Vapor Condensate.

Figure 1

Absolute (mg) and Relative (%) Spleen Weight in Female Sprague Dawley Rats Exposed to Baseline Gasoline Vapor Condensate (BGVC) via Inhalation for 5 Days per Week for 4 Weeks
Figure 2

Absolute (mg) and Relative (%) Thymus Weight in Female Sprague Dawley Rats Exposed to Baseline Gasoline Vapor Condensate (BGVC) via Inhalation for 5 Days per Week for 4 Weeks

Spleen IgM Antibody Response to the T-dependent Antigen, sRBC. Day 4 Response

The spleen IgM antibody-forming cell response, i.e. plaque assay, was evaluated on spleens removed 1 day after the last exposure, which was Day 4 after antigen sensitization. Day 4 after antigen sensitization is the peak day for the sRBC IgM AFC response in rats. Animals were sensitized in the morning and also sacrificed in the morning. The results of the AFC response are shown in Table 2 and in Figures 3 and 4. Viabilities were conducted on all cell suspensions using propidium iodide (PI) and the Coulter EPICS XL-MCL Flow Cytometer. The viabilities from all samples were greater than 95%.

In the plaque-forming cell (PFC) assays conducted by our laboratory and at the National Toxicology Program (NTP) Immunotoxicology Laboratory of the National Institute of Environmental Health Sciences, the PFC assay results are not adjusted for spleen cell viability. The reasons for this are as follows. In in vitro studies, which utilize a single population of cells, e.g. YAC-1 cells, correcting for viability is biologically meaningful. These cells, being of identical type, respond to stimuli in a similar manner and will die off at a similar rate. When spleens are utilized as the source of cells, this represents a heterogeneous mixture of cells, including...
neutrophils, lymphocytes, and macrophages. Each of these cell types will respond differently to stimuli under \textit{in vitro} conditions, i.e., neutrophils will die off at a faster rate than lymphocytes. Accordingly, conducting viability determinations on total spleen cells is of little biological value when one is evaluating antigen specific antibody production by plasma cells. More specifically, once the structural integrity of the spleen is compromised, as occurs in preparing a single cell suspension, the cells now in an \textit{in vitro} environment begin to die with the polymorphonuclear cells dying off at a much faster rate than will either lymphocytes or macrophages. The procedure utilized in our laboratory, and by the NTP Immunotoxicology Laboratory, minimizes the time it takes from preparing the single cell suspension of spleen cells to having them incubating in the assay petri dishes. By minimizing this preparation time, we also minimize the loss of viability, which occurs the longer the cells sit in the \textit{in vitro} cell culture conditions. The decrease in viability, which does occur during this time, is predominately due to the dying off of the more fragile polymorphonuclear cells and not the lymphocytes, particularly those antibody-forming cells (plasma cells) making antibody to sheep erythrocytes. This is due in part to the fact that cells undergoing high metabolic activities, such as rapidly proliferating cells or cells synthesizing antibody, are less susceptible to compounds which produce cell death than are quiescent cells. It is for these reasons that there is no correlation between viability of individual spleen cell preparations and their ability to produce antibodies to sheep erythrocytes. Correcting for viability for a homogenous population in \textit{in vitro} cultures is scientifically sound; however, as indicated above, using this procedure for mixed cell populations such as those present in the spleen, will result in artificially inflated PFC values.

There was no significant difference in the spleen cell number following exposure to Baseline Gasoline Vapor Condensate (Figure 3). The positive control, cyclophosphamide (CPS), produced an 82% decrease in spleen cell number when compared to the vehicle control group.

Shown in Table 2 and Figure 4 are the functional results from the IgM antibody-forming cell (AFC) assay. Shown in the left panel are the results when the data are expressed as specific activity and the results of the total spleen activity are shown in the right panel. As can be seen, there was no statistically significant difference in the IgM antibody-forming cell response between the Baseline Gasoline Vapor Condensate-exposed animals and the vehicle control group when evaluated either as specific activity (AFC/10^6 spleen cells) or as total spleen activity (AFC/spleen). Furthermore, there was no significant difference in the trend analysis when evaluated by the Jonckheere’s Test. This is a very liberal test, often demonstrating statistically significant results when there does not appear visually to be a dose-related trend or dose-related response. The fact that no statistically significant trend was detected with this liberal
test suggests that other statistical analysis for trend would have also shown a non-significant effect.

As anticipated, the positive control, CPS, produced a significant decrease in specific activity (100%) and total spleen cell activity (100%) when compared to the vehicle control animals. The results of the positive control were consistent with the historical controls for the laboratory. Similarly, the results of the negative control (vehicle) were also consistent with the historical controls for the laboratory.

Figure 3

Total Spleen Cell Numbers in Female Sprague Dawley Rats Exposed to Baseline Gasoline Vapor Condensate (BGVC) via Inhalation for 5 Days per Week for 4 Weeks
Exposure of female Sprague Dawley rats with Baseline Gasoline Vapor Condensate for a period of 5 days per week for 4 weeks did not result in alterations of the humoral immune response as evaluated in the IgM antibody-forming cell response to the T-dependent antigen sheep erythrocytes. There was no statistically significant effect on spleen weight, spleen cell number, or IgM antibody production when evaluated as either specific activity or as total spleen activity. Based on the immunological parameters evaluated, under the experimental conditions of the study, Baseline Gasoline Vapor Condensate did not adversely affect the immune response of female Sprague Dawley rats.
IX. REFERENCES


Table 1

Body Weight (g) and Organ Weights (mg) in Female Sprague Dawley Rats Exposed to Baseline Gasoline Vapor Condensate via Inhalation for 5 Days per Week for 4 Weeks

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<th>Parameter</th>
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<td></td>
<td>(10)</td>
<td>2000 (10) 10000 (10) 20000 (10)</td>
<td>(10)</td>
<td></td>
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<tr>
<td>Body Wgt (g)</td>
<td>247.8 ± 3.6</td>
<td>258.0 ± 5.2 250.0 ± 5.7 245.7 ± 2.7</td>
<td>224.4 ± 5.5**</td>
<td>H</td>
<td>NS</td>
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<tr>
<td>Spleen (mg)</td>
<td>615 ± 38</td>
<td>647 ± 26    600 ± 23    675 ± 102</td>
<td>265 ± 10**</td>
<td>NH</td>
<td>NS</td>
</tr>
<tr>
<td>% Body Wgt</td>
<td>0.248 ± 0.014</td>
<td>0.252 ± 0.012 0.239 ± 0.010 0.276 ± 0.041</td>
<td>0.119 ± 0.004**</td>
<td>NH</td>
<td>NS</td>
</tr>
<tr>
<td>Thymus (mg)</td>
<td>808 ± 33</td>
<td>761 ± 38    758 ± 44    724 ± 34</td>
<td>205 ± 14**</td>
<td>H</td>
<td>p ≤ 0.05</td>
</tr>
<tr>
<td>% Body Wgt</td>
<td>0.327 ± 0.013</td>
<td>0.297 ± 0.018 0.303 ± 0.018 0.293 ± 0.013</td>
<td>0.093 ± 0.006**</td>
<td>H</td>
<td>p ≤ 0.05</td>
</tr>
</tbody>
</table>

Female Sprague Dawley rats were administered vehicle control (air only) or Baseline Gasoline Vapor Condensate by inhalation via whole-body exposure for 5 days per week for 4 weeks. The positive control, cyclophosphamide, was administered i.p. on the last 4 days of exposure. On the day of sacrifice, spleens were placed in tubes containing media and sent to Richmond, VA, on ice pack for next day cell preparation. The rats were necropsied and indicated organ weighed. Values represent the mean ± SE derived from the number of animals indicated in parentheses. H = homogeneous data and NH = non-homogeneous data using the Bartlett's Test for homogeneity. Homogeneous data were evaluated using a parametric analysis of variance. When significant differences occurred, exposed groups were compared to the vehicle control group using the Dunnett's t Test. Non-homogeneous data were evaluated using a non-parametric analysis of variance. When significant differences occurred, exposed groups were compared to the vehicle control group using the Wilcoxon Rank Test. The positive control was compared to the vehicle control using the Student's t Test. Values significantly different from vehicle control at p ≤ 0.05 are indicated by an asterisk, while those significant at p ≤ 0.01 are noted by a double asterisk. The Jonckheere's Test was used to test for exposure level-related trends among the vehicle and exposed groups.

Key: g = grams; mg = milligrams; m³ = cubic meter of air; kg = kilograms; Wgt = weight; NS = not significant for p values greater than 0.05.
### Table 2

**Spleen Antibody-Forming Cell Response to T-dependent Antigen Sheep Erythrocytes in Female Sprague Dawley Rats Exposed to Baseline Gasoline Vapor Condensate via Inhalation for 5 Days per Week for 4 Weeks - Day 4 Response**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Body Wgt (g)</th>
<th>Spleen Wgt (mg)</th>
<th>Spleen Cells (x10^3)</th>
<th>IgM AFC/10^6 Spleen Cells</th>
<th>IgM AFC/Spleen (x 10^3)</th>
</tr>
</thead>
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<tr>
<td>Vehicle</td>
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<td>615 ± 38</td>
<td>53.18 ± 2.15</td>
<td>1639 ± 408</td>
<td>880 ± 209</td>
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<td>Baseline Gasoline Vapor</td>
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</tr>
<tr>
<td>2000 mg/m^3</td>
<td>258.0 ± 5.2</td>
<td>647 ± 26</td>
<td>62.26 ± 2.35</td>
<td>1540 ± 194</td>
<td>980 ± 143</td>
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<tr>
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<td>250.0 ± 5.7</td>
<td>600 ± 23</td>
<td>55.82 ± 4.02</td>
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<td>903 ± 120</td>
</tr>
<tr>
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<td>57.96 ± 3.33</td>
<td>1175 ± 111^a</td>
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<td>Cyclophosphamide</td>
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<td>50 mg/kg</td>
<td>224.4 ± 5.5**</td>
<td>265 ± 10**</td>
<td>9.69 ± 0.41**</td>
<td>3 ± 3**</td>
<td>0 ± 0**</td>
</tr>
</tbody>
</table>

| H/NH Trend Analysis       | NS           | NS              | NS                   | NS                       | NS                      |

Female Sprague Dawley rats were administered vehicle control (air only) or Baseline Gasoline Vapor Condensate by inhalation via whole-body exposure for 5 days per week for 4 weeks. The positive control, cyclophosphamide, was administered i.p. on the last 4 days of exposure. Four days prior to sacrifice, the rats were immunized (iv) with 2x10^8 sRBC. On the day of sacrifice, spleens were placed in tubes containing media and sent to Richmond, VA, on ice pack for next day cell preparation. Spleens were prepared into single cell suspensions and the number of IgM sRBC antibody-forming cells was determined. Values represent the mean ± SE derived from the number of animals indicated in parentheses. H = homogeneous data and NH = non-homogeneous data using the Bartlett's Test for homogeneity. Homogeneous data were evaluated using a parametric analysis of variance. When significant differences occurred, exposed groups were compared to the vehicle control group using the Dunnett's t Test. Non-homogeneous data were evaluated using a non-parametric analysis of variance. When significant differences occurred, exposed groups were compared to the vehicle control group using the Wilcoxon Rank Test. The positive control was compared to the vehicle control using the Student's t Test. Values significantly different from vehicle control at p ≤ 0.05 are indicated by an asterisk, while those significant at p ≤ 0.01 are noted by a double asterisk. The Jonckheere's Test was used to test for exposure level-related trends among the vehicle and exposed groups.

*Sprague Dawley rats, as a random bred strain, have inherently wide variability in their immune responses. However, it is the opinion of the PI based on his years of experience with this assay that one animal, which had an IgM AFC/10^6 value of 216 and an AFC/spleen of 123, was an outlier and it was scientifically appropriate not to include it in the analysis.

Key: g = grams; mg = milligrams; m^3 = cubic meter of air; kg = kilograms; Wgt = weight; NS = not significant for p values greater than 0.05.
APPENDIX A

INDIVIDUAL ANIMAL DATA
**INDIVIDUAL ANIMAL DATA**

**ORGAN WEIGHTS**

**BASELINE GASOLINE VAPOR CONDENSATE**

**00-6125**

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<th>THYMUS WGT (MG)</th>
<th>SPLEEN WGT/100 BODY WGT</th>
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APPENDIX B

CONTRACTING SPONSOR'S EXPOSURE AND ANIMAL DATA
INTRODUCTION: The following is data generated at Huntingdon Life Sciences, East Millstone, NJ. The separately issued main study report should be referenced for details of the procedures used for test atmosphere generation/characterization and animal evaluations.

STUDY DATES:  
Experimental Initiation Date: 13 December 2000 (in-life)  
Experimental Completion Date: 9 January 2001 (in-life)

EXPOSURES AND IN-LIFE SUMMARY: The actual measured results during the exposures were comparable to the targeted exposure levels. There were no exposure-related effects seen in the test animals with regards to body weights and feed consumption.

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## Chamber Monitoring Results

### Cumulative Exposure Record

**Group IB - 0 mg/m³ (Air Control)**

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### Table A
Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats

#### Chamber Monitoring Results
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| Chamber Environment Mean Humidity (%)     |       | 44.8 |
### Table A: Chamber Monitoring Results

**Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats**

**Group IIB - 2000 mg/m³**

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**Mean**

| 2563 | 2091 | 3.236 | 2.112 | 4.46E-03 | 22.3 | 47.9 |

**S.D.**

| 100  | 199  | 2.868 | 0.363 | 1.62E-03 | 1.0  | 6.3  |
### Table A
Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats

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Mean: 10080 | 10080 | 4.937 | 2.419 | 4.27E-03 | 23.2 | 46.1
S.D.: 366 | 1066 | 5.182 | 0.487 | 2.56E-03 | 0.9  | 4.9
### Table A
Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats

#### Chamber Monitoring Results

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Mean 10080 
S.D. 366

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### Chamber Environment
Mean Temperature: 22.7°C, Humidity: 47.8%
### Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats

#### Chamber Monitoring Results

**Cumulative Exposure Record**

Group IVA - 20000 mg/m$^3$

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**Table A**  
Baseline Gasoline Vapor Condensate: A 13-Week Whole-Body Inhalation Toxicity Study in Rats

**Chamber Monitoring Results**  
**Cumulative Exposure Record**  
**Group IVB - 20000 mg/m³**

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45.2  
S.D.  
341  
1599  
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0.157  
1.03E-03  
1.3  
8.0
TABLE B

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

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TABLE C

**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS**
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

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- **MEAN:** 118, 119, 119, 118, 118
- **S.D.:** 8.0, 8.3, 7.5, 7.9, 8.2
- **N:** 10

**WEEK 0**

- **MEAN:** 161, 163, 163, 163, 162
- **S.D.:** 7.5, 10.1, 9.8, 11.1, 10.3
- **N:** 10

**WEEK 1**

- **MEAN:** 185, 189, 186, 186, 188
- **S.D.:** 8.4, 12.8, 12.0, 8.8, 15.1
- **N:** 10

**WEEK 2**

- **MEAN:** 214, 218, 214, 209, 211
- **S.D.:** 8.4, 13.4, 13.0, 11.3, 18.7
- **N:** 10

**WEEK 3**

- **MEAN:** 236, 240, 237, 233, 233
- **S.D.:** 8.8, 15.1, 16.0, 10.7, 17.5
- **N:** 10

No statistically significant differences
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TABLE E

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

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No statistically significant differences
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BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

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CODE: 1-SLIGHT 2-MODERATE 3-MARKED P-PRESENT
### TABLE F

**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

**INDIVIDUAL WEEKLY CLINICAL OBSERVATIONS**

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- 2 = MODERATE
- 3 = MARKED
- P = PRESENT
### TABLE F

**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS**
**WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO**
**GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

**INDIVIDUAL WEEKLY CLINICAL OBSERVATIONS**

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**CODE:** 1-SLIGHT  2-MODERATE  3-MARKED  P-PRESENT
TABLE G

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL BODY WEIGHTS (GRAMS)

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N 10 10 10 10 10
### TABLE G

**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS**  
**WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO**  
**GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

**INDIVIDUAL BODY WEIGHTS (GRAMS)**

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**S.D.**

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## TABLE G

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL BODY WEIGHTS (GRAMS)

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TABLE H

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL BODY WEIGHT CHANGE (GRAMS)

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S.D.  3.4  5.3  7.7
N  10  10  10
**TABLE H**

**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS**

**WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO**

**GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

**INDIVIDUAL BODY WEIGHT CHANGE (GRAMS)**

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TABLE II

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL BODY WEIGHT CHANGE (GRAMS)

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N        10   10  10
TABLE H

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL BODY WEIGHT CHANGE (GRAMS)

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BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL BODY WEIGHT CHANGE (GRAMS)

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TABLE I

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS
WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL FEED CONSUMPTION VALUES (GRAMS/KG/DAY)

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N 9 10 10 9

SF=Spilled Feeder
### TABLE I

**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

**INDIVIDUAL FEED CONSUMPTION VALUES (GRAMS/KG/DAY)**

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**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

**INDIVIDUAL FEED CONSUMPTION VALUES (GRAMS/KG/DAY)**

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WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

INDIVIDUAL FEED CONSUMPTION VALUES (GRAMS/KG/DAY)

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INDIVIDUAL FEED CONSUMPTION VALUES (GRAMS/KG/DAY)

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MEAN: 135  106  95  91
S.D.:  3.5  4.8  3.3  3.2
N:     10   8   9   9

SF=Spilled Feeder
TABLE J

BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

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**BGVC: A 13-WEEK WHOLE-BODY INHALATION TOXICITY STUDY IN RATS**  
**WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO**  
**GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS**

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WITH NEUROTOXICITY ASSESSMENTS AND 4-WEEK IN VIVO
GENOTOXICITY AND IMMUNOTOXICITY ASSESSMENTS

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