1. Introduction

The Aloe vera (L.) Burm. f., plant (synonym = Aloe barbadensis Miller) is commonly referred to as aloe vera and belongs to the lily family (family Liliaceae, tribe Aloinae). This species is one of approximately 420 species of aloe (Burdock, 1997). The aloe plant is native to South Africa, but can also be found in dry sub-tropical and tropical climates, including the southern United States (Boudreau and Beland, 2006). The aloe vera plant has a long history of use for oral and topical applications. This publication describes safety studies conducted on a proprietary high-purity aloe vera inner leaf fillet preparation, Qmatrix®. In a 13-week study in rats, Qmatrix® was administered via gavage at 0, 500, 1000 and 2000 mg/kg body weight (bw)/day. There were no significant changes in food or water consumption, body weight, serum biochemistry or hematology at any of the doses tested. Sporadic, significant increases were observed in some of the measured urinalysis parameters; however, these variations were not treatment-related, as most were observed only in one sex, not dose-dependent and within historical control values. Organ weights were unaffected, except for a statistically significant, though not dose-dependent, increase in absolute and relative weights of the right kidney in males at 500 and 2000 mg/kg bw/day, respectively. Histopathological analysis revealed no abnormal signs. Qmatrix® was non-mutagenic in an Ames test and a chromosomal aberration test at concentrations up to 10,000 μg/plate, and in an in vivo bone marrow micronucleus test at doses up to 5000 mg/kg bw/day. Based on these results, Qmatrix® is not genotoxic in vitro or in vivo and has an oral NOAEL greater than 2000 mg/kg bw/day following 90 days of oral exposure.

Safety studies conducted on a proprietary high-purity aloe vera inner leaf fillet preparation, Qmatrix®

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Abstract

The aloe vera plant has a long history of safe use for oral and topical applications. This publication describes safety studies conducted on a proprietary high-purity aloe vera inner leaf fillet preparation, Qmatrix®. In a 13-week study in rats, Qmatrix® was administered via gavage at 0, 500, 1000 and 2000 mg/kg body weight (bw)/day. There were no significant changes in food or water consumption, body weight, serum biochemistry or hematology at any of the doses tested. Sporadic, significant increases were observed in some of the measured urinalysis parameters; however, these variations were not treatment-related, as most were observed only in one sex, not dose-dependent and within historical control values. Organ weights were unaffected, except for a statistically significant, though not dose-dependent, increase in absolute and relative weights of the right kidney in males at 500 and 2000 mg/kg bw/day, respectively. Histopathological analysis revealed no abnormal signs. Qmatrix® was non-mutagenic in an Ames test and a chromosomal aberration test at concentrations up to 10,000 μg/plate, and in an in vivo bone marrow micronucleus test at doses up to 5000 mg/kg bw/day. Based on these results, Qmatrix® is not genotoxic in vitro or in vivo and has an oral NOAEL greater than 2000 mg/kg bw/day following 90 days of oral exposure.

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agent for abrasions and burns and to promote healing of dermal ulcers, wounds and frostbite (Boudreau et al., 2005). Aloe vera has been suggested to possess anti-cancer, anti-viral, anti-inflammatory, anti-diabetic and anti-bacterial properties; however, the mechanism(s) of these proposed effects is not fully understood (Leung and Foster, 1996; Evans, 2002). Aloe extracts have also been used for many years as an ingredient in a variety of personal care and cosmetic products, such as face and hand creams, cleansers, soaps, suntan lotions, shampoos and hair tonics, shaving preparations, bath aids, makeup and fragrance preparations, skin moisturizers, baby lotions and wipes (Boudreau and Beland, 2006; Andersen, 2007). In addition to these uses, several species of aloe (A. barbadensis, A. perryi, A. ferox and hybrids of A. ferox with A. africana and A. saccharina) are approved by the US Food and Drug Administration (FDA) for use in human food as natural flavoring agents and in over-the-counter (OTC) drugs, dietary supplements and cosmetic products (FDA, 2008).

Despite aloe vera’s long history of use, several toxicity studies in the scientific literature have reported contrasting results, with some suggesting that aloe vera possesses toxic potential and others reporting no adverse effects. In these studies, various aloe preparations were utilized, including crude, poorly characterized extracts of the A. vera and A. ferox plants, or constituents of the aloe vera plant of varying purity. These studies included single and repeated dose studies in which the test materials were administered orally or via intraperitoneal or intravenous injections, as well as in vitro and in vivo genotoxicity studies (Andersen, 2007). Boudreau and Beland (2006) indicated that one possible reason for these conflicting results is the difficulty in clearly differentiating the plant part and the species utilized in these studies. Also, the method of production may result in the inclusion of products of the outer pulp (just inside the cuticle and containing the pericyclic cells), which contains a variety of anthraquinones (including, but not limited to aloins A and B, alo-emodin and diacetylbetin). The sum of the two aloins (A and B), called barbaloin, is the predominant anthraquinone(s) and, aloin content is therefore the marker indicating the presence of anthraquinones (Andersen, 2007).

The disparate and incongruous results of previous studies led the authors to believe the problem may lie with test substances and in vivo genotoxicity studies (Andersen, 2007). Boudreau and Beland (2006) indicated that one possible reason for these conflicting results is the difficulty in clearly differentiating the plant part and the species utilized in these studies. Also, the method of production may result in the inclusion of products of the outer pulp (just inside the cuticle and containing the pericyclic cells), which contains a variety of anthraquinones (including, but not limited to aloins A and B, alo-emodin and diacetylbetin). The sum of the two aloins (A and B), called barbaloin, is the predominant anthraquinone(s) and, aloin content is therefore the marker indicating the presence of anthraquinones (Andersen, 2007).

The test material, Qmatrix®, aloe vera inner leaf fillet (hereinafter referred to as Qmatrix®) that was used in these subchronic and genotoxicity studies, is a white to light tan powder derived from mucilaginous parenchymal cells found in the inner central area of the aloe vera leaf (commonly referred to as aloe vera gel, inner leaf gel or inner leaf fillet), which has a very low level of anthraquinones. These studies were conducted in compliance with GLP and OECD guidelines.  

### 2. Materials and methods

#### 2.1. Test material

The test material, Qmatrix®, aloe vera inner leaf fillet (hereinafter referred to as Qmatrix®) that was used in these subchronic and genotoxicity studies, is a white to light tan powder derived from mucilaginous parenchymal cells found in the inner central area of the A. vera (L) leaf (Aloecorp, Inc., Lacey, WA). Qmatrix® is manufactured using a proprietary extraction process in which the aloe latex contaminant (containing anthraquinones) is substantially reduced (including aloin, aloeresin A), as determined by the method of Zahn et al. (2007). A single lot of Qmatrix® (No. G7304B15) was used in all studies and conforms to Qmatrix® specifications (Table 1).

#### 2.2. Bacterial reverse mutation test (Ames test)

Qmatrix® was evaluated for mutagenic activity in the bacterial reverse mutation test using standard Salmonella typhimurium direct plate incorporation method in accordance with OECD guideline number 471 “Bacterial Reverse Mutation Test”. The vehicle (distilled water) was used as the negative control and 2-aminoanthracene, sodium azide, 4-nitroquinoline-N-oxide, 9-aminoacridine and acridine mutagens were used as positive controls. The potential for mutagenicity was assessed in S. typhimurium tester strains TA98, TA100, TA1535, TA1537 and Escherichia coli tester strain WP2 uvrA. The tester strains were incubated with Qmatrix® (dissolved in sterile distilled water) at concentrations of 185, 556, 1112, 2224 and 2560 μg/ml. The tester strains were incubated with Qmatrix® for 48 hours at 37°C and the revertant colonies were counted.

#### 2.3. In vitro mammalian chromosome aberration test

Qmatrix® was evaluated for mutagenic potential in Chinese Hamster Lung (CHL) cells, in accordance with OECD guideline number 473 “Standard Chromosome Aberration Test.” The vehicle (complete culture media) was used as the negative control and cyclophosphamide and ethylmethanesulfonate were used as positive controls. Genotoxicity was assessed in the presence and absence of metabolic activation (S9). The potential mutagenicity of Qmatrix® was evaluated in two experiments in which the cells were exposed to the test material at short-term (6 h) and long-term (24 h) exposure periods at concentrations of 2500, 5000 and 10,000 μg/ml.

#### 2.4. Mouse micronucleus test

Qmatrix® was evaluated for mutagenic potential in mouse bone marrow cells and in accordance with the OECD guideline 474 “Mammalian Erythrocyte Micronucleus Test.”
2.4.1. Animals
Adult ICR mice (7-weeks-old) were obtained from Koatec Co. (Gyeonggi, Korea). Animals were housed in polycarbonate cages with Aspen chips bedding (ABEDD Baltic SIA, Atlantijas iela 23, Riga 1015, Latvia; analyzed prior to use for pesticides, heavy metals and microbiological load). A standardized diet was provided (Harlan Co., Ltd, USA. Teklad Certified Global 18% Protein Rodent Diet, 2918C), and the animals were held in a controlled 12-h light/dark cycle. Temperature was maintained at 20–26 °C with a relative humidity of 40–70%. Potable water and standardized diet were provided ad libitum.

2.4.2. Experimental procedure
In a preliminary range-finding mouse micronucleus study, male and female ICR mice (2/sex/group) were administered Qmatrix® via gavage in sterile distilled water at doses of 0, 2500 and 5000 mg/kg bw/day for two consecutive days; dosing volume was 20 ml/kg bw/day for all groups. The animals were observed daily for mortality and clinical signs of toxicity and were sacrificed 24 h following the second test article administration. There was no mortality or clinical signs of toxicity in any of the dose groups in either sex; therefore, in the main study only male mice were utilized. In the main study, groups of male ICR mice (six per group) were administered the Qmatrix® in sterile distilled water via gavage at doses of 1250, 2500 and 5000 mg/kg/day once daily for two consecutive days. A positive control group was administered cyclophosphamide once via intraperitoneal injection on the second day of the Qmatrix® dosing schedule. A negative control group was administered sterile distilled water via gavage. The animals were observed daily for clinical signs and mortality and were euthanized 24 h following the second test article administration. Body weight was measured prior to study initiation, at dosing and necropsy. Bone marrow samples were collected from the femur of each animal and two bone marrow smears per animal were prepared for analysis. For each animal, the number of micronucleated polychromatic erythrocytes (MNPC) was counted in 2000 polychromatic erythrocytes (PCE). The PCE/(PCE + NCE) ratio was determined after scoring 500 erythrocytes.

2.5. 13-Week study
The potential toxicity of Qmatrix® was evaluated in a subchronic toxicity study in rats conducted in accordance with OECD Guideline 408 “Repeated Dose 90 Day Oral Toxicity Study in Rodents.”

2.5.1. Animals
Sprague–Dawley rats were supplied from Koatec Co. (Gyeonggido, Korea), and were 6–7 weeks of age at the beginning of the study. The animals were housed singly in an animal room with a 12-h light/dark cycle and temperature was maintained at 20–26 °C with a relative humidity of 40–70%. The animals were acclimated for 7 days prior to testing. The same bedding and diet was used as in the previously described mouse study. Potable water and diet were provided ad libitum.

2.5.2. Experimental procedure
Four groups of 20 rats (10/sex/group) were administered Qmatrix® in sterile distilled water orally via gavage at doses of 0 (control), 500, 1000, or 2000 mg/kg bw/day for 13 weeks; dosing volume was 10 ml/kg bw/day for all groups. The animals were observed daily for mortality and signs of gross toxicity. Food and water consumption was recorded weekly. Body weights were recorded prior to test initiation, weekly during the study, and just prior to terminal sacrifice. Ophthalmic examinations using an ophthalmoscope and a fundus camera were conducted before the beginning of treatment and during week 13 on animals in the control and high-dose group.

Urine samples were collected from each animal at week 13, the measured volumes were then analyzed for pH, ketone, color, glucose, bilirubin, specific gravity, blood, protein, urobilinogen, nitrate and leukocytes on a Clinitek® Automated Urine Chemistry analyzer (Siemens Medical Solutions Diagnostics, Tarrytown, NY).

Blood samples were collected from each animal at necropsy for hematology and clinical chemistry. Blood samples were collected from the posterior vena cava and EDTA was used as an anticoagulant. Animals were fasted overnight prior to collection of samples. Hematological parameters measured included white blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, hemoglobin concentration distribution width, red cell count, red blood cell distribution width, platelet count, mean platelet volume, reticulocyte, differential white blood cell count.

Clinical biochemistry values analyzed were: alanine aminotransferase, albumin, albumin/globulin ratio, alkaline phosphatase, aspartate aminotransferase, bilirubin, blood creatinine, blood urea nitrogen, calcium, chloride, creatine phosphokinase, fasting glucose, globulin, inorganic phosphorus, potassium, sodium, total cholesterol, total serum protein and triglycerides. Prothrombin time and active partial thromboplastin time were also measured to evaluate blood clotting time.

Animals were euthanized with ether and underwent a detailed necropsy. All animals were subjected to a full macroscopic examination of tissues. All external features and orifices were visually examined. The thoracic, abdominal and pelvic cavities and their viscera were also examined. The adrenal glands, brain, epididymis, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, spleen, testes and thymus were weighed and examined microscopically. Testes and epididymides were fixed in Bouin’s solution and the eyes were fixed in Davidson’s fluid. The seminal vesicles, prostate, ovaries, uterus, vagina, urinary bladder, spleen, stomach, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, mesenteric lymph node, adrenal gland, kidney, liver, skeletal muscle, sciatic nerve, femur, mandibular lymph node, salivary gland, sternum, thymus, heart, lung, aorta, thoracic spinal cord, tongue, trachea, esophagus, thyroid gland, brain, pituitary gland and mammary glands were preserved in 10% neutral buffered formalin. The fixed organs and tissues from the control and high-dose groups were evaluated for histological changes following staining with hematoxylin and eosin and examination by light microscopy.

2.5.3. Statistical analysis
Statistical analysis of the in-life and organ weight data (i.e., means and standard deviations of body weight, daily food and consumption, absolute and relative organ weights, hematology and serum biochemistry parameters) were initially subjected to a One-Way Analysis of Variance (ANOVA). If the results were significant, the Levene test was performed to evaluate the variance homogeneity. When the variances were homogenous, treated and control groups were compared using the Duncan’s multiple range test. When the variances were not homogeneous, treated and control groups were compared using the Dunnett’s T-test.

For the urinalysis results, data which expressed the severity of the observed signs were ranked, as shown in Table 2, and the groups were compared using a non-parametric method (Kruskal-Wallis non-parametric analysis of variance). If significant, the Mann–Whitney U-test was conducted for comparison with the values from the vehicle control group. Fisher’s exact test was applied to the urine color test.

Table 3
Reverse mutation assay with Qmatrix® in the absence or presence of S9 mix.

<table>
<thead>
<tr>
<th>Concentration (µg/plate)</th>
<th>TA98</th>
<th>TA100</th>
<th>TA1535</th>
<th>TA1537</th>
<th>WP2uvrA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−S9</td>
<td>+S9</td>
<td>−S9</td>
<td>+S9</td>
<td>−S9</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>25</td>
<td>116</td>
<td>118</td>
<td>11</td>
</tr>
<tr>
<td>185</td>
<td>20</td>
<td>28</td>
<td>120</td>
<td>114</td>
<td>12</td>
</tr>
<tr>
<td>556</td>
<td>19</td>
<td>29</td>
<td>120</td>
<td>114</td>
<td>12</td>
</tr>
<tr>
<td>1667</td>
<td>21</td>
<td>30</td>
<td>104</td>
<td>117</td>
<td>12</td>
</tr>
<tr>
<td>5000</td>
<td>23</td>
<td>26</td>
<td>110</td>
<td>104</td>
<td>14</td>
</tr>
<tr>
<td>10,000</td>
<td>27</td>
<td>27</td>
<td>111</td>
<td>113</td>
<td>11</td>
</tr>
<tr>
<td>Positive control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>20</td>
<td>25</td>
<td>309</td>
<td>445</td>
<td>234</td>
</tr>
<tr>
<td>1.0</td>
<td>20</td>
<td>25</td>
<td>309</td>
<td>445</td>
<td>234</td>
</tr>
<tr>
<td>2.0</td>
<td>50</td>
<td>50</td>
<td>95</td>
<td>754</td>
<td>58</td>
</tr>
</tbody>
</table>

*−S9/+S9 = Colonies/plate [factor] – No. of colonies of treated plate/No. of colonies of negative control plate.

a 2-Aminoanthracene.
b Sodium azide.
c 4-Nitroquinoline N-oxide.
d 9-Aminoacridine.
e Acridine mutagen ICR 191.
rats, water consumption was significantly increased at 1000 (p < 0.05) and 2000 mg/kg bw/day (p < 0.01) on week 1. However, over the entire duration the 13-week study, total water consumption in the Qmatrix® treatment groups was not significantly different from the controls. There were no statistically significant differences between the control and treated animals in the measured serum biochemistry (Table 7), and hematological parameters were comparable between control and Qmatrix®-treated animals, except for a significant increase in monocytes which was only observed in males at 2000 mg/kg bw/day. The increase in monocytes in males was only observed in one sex and was therefore not considered to be treatment related.

Evaluation of urinalysis parameters revealed a tendency in both males and females for protein, leukocytes, specific gravity and pH results to be slightly higher in the Qmatrix®-treated animals as compared to the controls. In females at all dose levels, specific gravity and pH values were significantly higher than control values and protein was significantly higher at 1000 and 2000 mg/kg bw/day as compared to the controls (Table 8), although the increased specific gravity is likely explained in part by the low urine volume.
in the mid and high dose females. In males, ketone bodies and protein at 500 and 2000 mg/kg bw/day and leukocytes at 1000 mg/kg bw/day were significantly higher than control values. Urine volume was significantly decreased in females at 2000 mg/kg bw/day as compared to the controls. In contrast, urine volume was significantly increased in the 2000 mg/kg bw/day male dose group, as compared to the controls.

With the exception of the increased protein value mentioned above, there is no comparable finding in the opposite sex and for many (most) of the differences in treated animal urine values (compared to control) likewise, there is no dose–response relationship, nor is there a corroborative clinical chemistry or histopathological change for the difference(s) reported. In addition, all of these values are within the range of historical control values for this strain of rat. Lastly, at least some of the findings of statistical significance between the same values (zero in most cases), may be an artifact of the analysis. Therefore, the authors do not believe these findings are relevant to the determination of safety for Qmatrix.

There were no statistically significant differences in organ weights between the control and treated animals except for statistically significant increases in absolute weight of the right kidney in males at 500 mg/kg bw/day and relative weight of the right kidney in males at 2000 mg/kg bw/day (Table 9). The left and right kidneys of the females rats in all dose groups were unaffected by treatment with Qmatrix®.
### Table 9

**Absolute and relative organ weights of male and female rats administered Qmatrix® for 13 weeks.**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Males (0 mg/kg/day)</th>
<th>500 mg/kg/day</th>
<th>1000 mg/kg/day</th>
<th>2000 mg/kg/day</th>
<th>Females (0 mg/kg/day)</th>
<th>500 mg/kg/day</th>
<th>1000 mg/kg/day</th>
<th>2000 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body weights</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal body weight</td>
<td>452.14 ± 27.46</td>
<td>474.21 ± 19.20</td>
<td>453.92 ± 18.68</td>
<td>447.69 ± 27.90</td>
<td>263.87 ± 27.95</td>
<td>253.56 ± 11.32</td>
<td>257.52 ± 15.49</td>
<td>250.23 ± 11.32</td>
</tr>
<tr>
<td>Adrenal gland L. (g)</td>
<td>0.0279 ± 0.0050</td>
<td>0.0283 ± 0.0044</td>
<td>0.0277 ± 0.0030</td>
<td>0.0281 ± 0.0043</td>
<td>0.0325 ± 0.0053</td>
<td>0.0311 ± 0.0030</td>
<td>0.0301 ± 0.0021</td>
<td>0.0306 ± 0.0020</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.0062 ± 0.0012</td>
<td>0.0069 ± 0.0010</td>
<td>0.0061 ± 0.0005</td>
<td>0.0063 ± 0.0009</td>
<td>0.0124 ± 0.0022</td>
<td>0.0123 ± 0.0012</td>
<td>0.0117 ± 0.0012</td>
<td>0.0123 ± 0.0009</td>
</tr>
<tr>
<td>Adrenal gland R. (g)</td>
<td>0.0276 ± 0.0036</td>
<td>0.0279 ± 0.0033</td>
<td>0.0276 ± 0.0038</td>
<td>0.0272 ± 0.0042</td>
<td>0.0295 ± 0.0040</td>
<td>0.0299 ± 0.0032</td>
<td>0.0299 ± 0.0035</td>
<td>0.0300 ± 0.0034</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.0061 ± 0.0010</td>
<td>0.0059 ± 0.0007</td>
<td>0.0061 ± 0.0008</td>
<td>0.0061 ± 0.0009</td>
<td>0.0112 ± 0.0020</td>
<td>0.0118 ± 0.0012</td>
<td>0.0117 ± 0.0016</td>
<td>0.0120 ± 0.0015</td>
</tr>
<tr>
<td>Pituitary gland (g)</td>
<td>0.0118 ± 0.0014</td>
<td>0.0121 ± 0.0013</td>
<td>0.0121 ± 0.0014</td>
<td>0.0119 ± 0.0010</td>
<td>0.0129 ± 0.0012</td>
<td>0.0124 ± 0.0013</td>
<td>0.0127 ± 0.0013</td>
<td>0.0126 ± 0.0014</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.0026 ± 0.0003</td>
<td>0.0026 ± 0.0003</td>
<td>0.0027 ± 0.0003</td>
<td>0.0027 ± 0.0001</td>
<td>0.0049 ± 0.0005</td>
<td>0.0049 ± 0.0004</td>
<td>0.0050 ± 0.0006</td>
<td>0.0051 ± 0.0006</td>
</tr>
<tr>
<td>Thymus (g)</td>
<td>0.2653 ± 0.0348</td>
<td>0.3062 ± 0.0657</td>
<td>0.2793 ± 0.0530</td>
<td>0.2912 ± 0.0503</td>
<td>0.2565 ± 0.0613</td>
<td>0.2330 ± 0.0275</td>
<td>0.2106 ± 0.0369</td>
<td>0.2390 ± 0.0614</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.0588 ± 0.0079</td>
<td>0.0645 ± 0.0125</td>
<td>0.0615 ± 0.0113</td>
<td>0.0649 ± 0.0099</td>
<td>0.0965 ± 0.0151</td>
<td>0.0919 ± 0.0104</td>
<td>0.0819 ± 0.0141</td>
<td>0.0954 ± 0.0243</td>
</tr>
<tr>
<td>Prostate (g)</td>
<td>0.8682 ± 0.1610</td>
<td>0.6752 ± 0.1564</td>
<td>0.5614 ± 0.1207</td>
<td>0.6186 ± 0.1699</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.1516 ± 0.0354</td>
<td>0.1424 ± 0.0324</td>
<td>0.1235 ± 0.0225</td>
<td>0.1389 ± 0.0402</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Testis Lt. (g)</td>
<td>2.0140 ± 0.9961</td>
<td>2.0847 ± 0.1641</td>
<td>2.0374 ± 0.0934</td>
<td>2.0794 ± 0.1479</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.4466 ± 0.0302</td>
<td>0.4393 ± 0.0234</td>
<td>0.4495 ± 0.0279</td>
<td>0.4654 ± 0.0342</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Testis Rt.</td>
<td>2.0392 ± 0.1014</td>
<td>2.0740 ± 0.1584</td>
<td>2.0335 ± 0.0980</td>
<td>2.0622 ± 0.1606</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.4524 ± 0.0331</td>
<td>0.4371 ± 0.0238</td>
<td>0.4486 ± 0.0272</td>
<td>0.4611 ± 0.0293</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ovary Lt. (g)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.0469 ± 0.0118</td>
<td>0.0407 ± 0.0106</td>
<td>0.0421 ± 0.0096</td>
<td>0.0444 ± 0.0057</td>
</tr>
<tr>
<td>% of body weight</td>
<td>0.0177 ± 0.0033</td>
<td>0.0160 ± 0.0040</td>
<td>0.0164 ± 0.0039</td>
<td>0.0177 ± 0.0019</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ovary Rt. (g)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.0450 ± 0.0075</td>
<td>0.0381 ± 0.0135</td>
<td>0.0445 ± 0.0079</td>
<td>0.0428 ± 0.0050</td>
</tr>
<tr>
<td>% of body weight</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.0171 ± 0.0029</td>
<td>0.0150 ± 0.0052</td>
<td>0.0173 ± 0.0030</td>
<td>0.0171 ± 0.0017</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>11.2395 ± 0.8659</td>
<td>12.2369 ± 0.7849</td>
<td>11.2629 ± 0.9273</td>
<td>11.2441 ± 1.1662</td>
<td>6.1702 ± 0.6942</td>
<td>6.3243 ± 0.4771</td>
<td>6.0588 ± 0.5365</td>
<td>5.9796 ± 0.7201</td>
</tr>
<tr>
<td>% of body weight</td>
<td>2.4859 ± 0.1170</td>
<td>2.5813 ± 0.1494</td>
<td>2.4790 ± 0.1327</td>
<td>2.5079 ± 0.1496</td>
<td>2.3418 ± 0.1704</td>
<td>2.4953 ± 0.1670</td>
<td>2.3509 ± 0.1175</td>
<td>2.3899 ± 0.0753</td>
</tr>
</tbody>
</table>

**Notes:**
- Body weights right before necropsy, after fasting.
- N = 10/sex/group.
- Significant difference at p < 0.05 level compared with the vehicle control.
- Significant difference at p < 0.01 level compared with the vehicle control.

*ARTICLE IN PRESS*
arations of the aloe vera plant and its constituents. In a 90 day sub-chronic toxicity study, male Swiss albino mice were orally adminis-
tered a crude, ethanol extract of the aerial portion of the aloe vera plant (species not indicated) in drinking water at a dose of 100 mg/ kg bw/day for 90 days (Shah et al., 1989). It was reported that six of the 20 animals dosed with aloe vera extract died during the study and that 20% of the treated animals experienced alopecia of the genital area and degeneration and putrification of the sex organs. Also, 10% of the treated animals had inflammation of the hind limb and there was a statistically significant decrease in red blood cell counts in the aloe vera-treated animals as compared to the controls. The overall relevance of the results of this study is question-
able, because chemical composition (including purity and potential contaminants) of the extract were not specified and, that these test results are inconsistent with other studies.

Herlihy et al. (1998) administered two aloe vera (Aloe barbaden-
sis) preparations at 1% and 10% in the diet (approximately equiva-
lent to 500 and 5000 mg/kg bw/day, respectively) to male Fischer 344 rats (five per group) for 1.5 or 5.5 months. The first preparation (A1 and A10) was prepared from homogenized aloe filets from the inner leaf of the plant, which were then lyophilized and frozen prior to mixing with the diets. The second preparation (B1 and B10) was prepared in an identical manner as preparation A, except that the aloe filet homogenate was charcoal filtered prior to lyoph-
ilization to more closely resemble commercial products. Due to re-
ported diarrhea and a reduction in growth rate, the concentration of preparation A10 was reduced from 10% to 5% and 3% in the diet however, despite these successive reductions in dose, the reduced growth rate and diarrhea persisted therefore the A10 group was eliminated from the study. In the groups fed preparations A1 and B1 and B10, there were no reported adverse effects on body weight, food consumption or organ weights. Also, there were no changes in serum chemistry, except for statistically significant decreases in aspartate aminotransferase at all dosages and alanine aminotrans-
ferase in preparations A1 and B10 as compared to the control group (p < 0.05). Also, serum cholesterol and high-density lipoproteins were significantly decreased in preparation B10 as compared to the control group (p < 0.05). Gross and histopathological analy-
sis of organs revealed no treatment-related adverse effects in the animals fed either preparation. The authors stated that the effects observed in preparation A10 may have been due to the presence of the anthraquinone, barbaloin, which has been shown to have cathartic effects. This suggestion was supported by the lack of diar-
rhea or reduced growth rates in animals fed preparation B in which anthraqui-nones were removed by charcoal filtration. The authors concluded that long-term ingestion of the aloe vera preparations A and B are safe at concentrations up to 1% in the diet (500 mg/ kg bw/day).

In a 90-day study conducted with acemannan, the primary polysaccharide constituent of aloe vera inner leaf, Beagle dogs were fed acemannan in the diet at doses of 0, 100, 400 and 1500 mg/kg/day (Fogelman et al., 1992). Food consumption and body weight was measured throughout the study period and oph-
thalnic examinations and hematology, serum chemistry and urinal-
alysis determinations were performed. The results revealed no mortality or significant signs of systemic toxicity at any of the doses tested.

Fogelman et al. (1992) also administered acemannan to Sprague-Dawley rats in the diet at doses of 0, 200, 650 and 2000 mg/ kg/day for 6 months. Evaluation of the same toxicological end-
points as in the dog study was evaluated and there was no reported mortality or adverse effects in any of the measured parameters at any of the doses tested.

In addition, several studies have evaluated the potential geno-
toxicity of various preparations of aloe vera and its constituents. In a gene mutation (rec assay) test conducted with Bacillus subtilis,
cells were exposed to Qmatrix® at concentrations up to 10,000 µg/ml for 4–48 h. Qmatrix® did not exhibit any mutagenic activity in any of the strains utilized at any of the concentrations tested. In an in vitro mouse micronucleus test in rats at doses up to 5000 mg/kg bw, Qmatrix® did not cause any genotoxic effects at any of the doses tested.

Therefore, based on the totality of evidence, including our empirical observations presented herein and reports in the scientific literature, we have concluded that Qmatrix® is non-genotoxic in vitro or in vivo and the NOAEL in the subchronic toxicity study is greater than 2000 mg/kg bw/day.

References


