GRAS NOTIFICATION FOR SOY LEGHEMOGLOBIN PROTEIN PREPARATION DERIVED FROM *PICHIA PASTORIS*

Submitted by:
Impossible Foods Inc.
525 Chesapeake Drive
Redwood City, CA 94063

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PART 1: SIGNED STATEMENTS AND CERTIFICATIONS

1. This GRAS notice is submitted in accordance with 21 C.F.R. Part 170, Subpart E.

2. Name and Address of Submitting Company:
   Impossible Foods Inc.
   525 Chesapeake Drive
   Redwood City, CA 94063
   Phone: (650) 461-4385

3. Name of Notified Substance: Soy leghemoglobin protein preparation

4. Intended Conditions of Use:
   a. List of foods and/or drinking water to be added to: Ground beef analogue products.

   b. Proposed levels of use: Soy leghemoglobin protein preparation will be added to the ground beef analogue product to deliver not more than 0.8% soy leghemoglobin protein.

   c. Purpose of substance in the food product: The primary purpose of the characterizing component of soy leghemoglobin protein preparation, soy leghemoglobin protein, is to create a flavor impact in ground beef analogue products. In addition, soy leghemoglobin protein has a nutritive value as a source of iron, analogous to the role of myoglobin as an iron source in meat.

   d. Subpopulation expected to consume product: (if appropriate): No subpopulations are anticipated.

5. Statutory Basis for GRAS Conclusion:
   The statutory basis for the GRAS conclusion for soy leghemoglobin protein preparation is scientific procedures. Impossible Foods has assembled the scientific data to conclude that soy leghemoglobin protein preparation is generally recognized as safe for use as a component of ground beef analogue products.

6. It is the view of Impossible Foods that the substance is not subject to premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on Impossible Foods' conclusion that soy leghemoglobin preparation is GRAS for the intended use as a component of ground beef analogue products.

7. Availability of Information for FDA Review: The data and information that are the basis for Impossible Foods GRAS determination are available for FDA's review, and copies will be sent to FDA upon request, in either electronic format or by paper copy. Requests for copies and arrangements for review of materials cited herein may be directed to:

Gary L. Yingling
Morgan, Lewis and Bockius, LLP
1111 Pennsylvania Ave, NW
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8. Exemptions from FOIA Disclosure:
   The information provided in this application does not contain confidential or proprietary information, and therefore no FOIA exemptions are claimed.

9. Authorization to Share Trade Secrets with FSIS:
   Should FDA find the need to share the information in this application with FSIS, Impossible Foods has no objections.

10. Certification
    On behalf of Impossible Foods, I certify that, to the best of my knowledge, the GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to me and Impossible Foods, and pertinent to the evaluation of the safety and GRAS status of soy leghemoglobin protein preparation for use as a component of ground beef analogue products.

    Signed:

    (b) (6) [redacted]

    10/02/2017

    Gary L. Yingling — Date
    Senior Counsel
    Morgan, Lewis, and Bockius LLP

PART 2: IDENTITY OF THE NOTIFIED SUBSTANCE

2.1. Chemical Name

The preparation containing soy leghemoglobin protein (along with other components) that is used as a food ingredient in Impossible Foods Inc. ("Impossible Foods") ground beef analogue products is referred to as "LegH Prep".

Soy leghemoglobin protein (UniProtKB/Swiss-Prot #: P02236, GeneInfo Identifier (GI) 126241) is the chemical name of the characterizing component of LegH Prep. The source of soy leghemoglobin protein is the soy plant *Glycine max* gene *LGB2*. Soy leghemoglobin protein is found in the root nodules of the soy plant.

In this report, the terms "soy leghemoglobin" and "soy leghemoglobin protein" are used interchangeably to refer to the characterizing component of LegH Prep.

2.2. Common or Usual Name

As discussed in greater detail in other sections of this GRAS notification, Impossible Foods has determined that the use of LegH Prep as a component of ground beef analogue products is generally recognized as safe.

According to the section 403(I)(2) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 101.4, a food product must list the common or usual name of each ingredient in the food. Impossible Foods recognizes, in this GRAS notification, that an appropriate common or usual name for the LegH Prep used in its products is "leghemoglobin (soy)". Impossible Foods will include "soy" on the label. In addition, Impossible Foods will notify consumers that the product "Contains Soy" as required by the statute.

2.3. Applicable Conditions of Use

LegH Prep, a mixture containing soy leghemoglobin protein, *Pichia* (yeast) proteins, sodium chloride, and sodium ascorbate, is to be used as a plant-based protein component in nonanimal-derived food products with the texture, nutrition, flavor and aroma of traditional animal-derived foods.

LegH Prep, along with several other Food and Drug Administration ("FDA" or "Agency") recognized plant proteins, will be components of the ground beef analogue products. Other proteins may include, but are not limited to, commercially available proteins from soy, pea, mung bean, lentil, corn, potato and wheat. LegH Prep will function to catalyse flavor chemistry and contribute to the nutritional quality of ground beef analogue products. A typical ground beef analogue product will contain:

Component	Ground Beef Analogue
Protein	10%-25%
Oils	0%-25%
Miscellaneous[1]	2%
Water	50%-75%

[1]Miscellaneous ingredients include salt, flavors, vitamins, essential amino acids, etc.

2.3.1 Levels of Use

LegH Prep will be added to the ground beef analogue product to deliver not more than 0.8% soy leghemoglobin protein. The use of LegH Prep in ground beef analogue products is self-limiting based on unacceptable organoleptic properties at higher levels.

2.3.2 Purposes

The primary purpose of the characterizing component, soy leghemoglobin protein, in LegH Prep is to create a flavor impact in ground beef analogue products. In addition, soy leghemoglobin has a nutritive value as a source of iron, analogous to the role of myoglobin as an iron source in meat. Once cooked and digested, both soy leghemoglobin and animal-based myoglobin release identical heme B molecules into the digestive system (Annex 1). Studies using cell models of iron bioavailability have shown that the bioavailability of iron in soy leghemoglobin is equivalent to that of bovine myoglobin when in a food-like substrate (Proulx & Reddy, 2006). Thus, the use of LegH Prep in ground beef analogue products will enhance both the flavor and the dietary profile of those products (Carpenter & Mahoney, 1992).

2.4. Composition

Hemoglobin proteins are found in most organisms, including bacteria, protozoa, fungi, plants and animals (Hardison, 1998). Hemeproteins are classified as globin/non-globin and symbiotic/non-symbiotic. Hemoglobin, myoglobin, and leghemoglobin are examples of globin proteins. Cytochrome oxidases, hemocyanins, and methemalbumin are examples of non-globin hemeproteins (Everse, 2004; Jokipii-Lukkari, 2009). Plant hemoglobins are classified according to function as symbiotic or non-symbiotic (Gupta, 2011). Symbiotic hemoglobins are found predominantly in legumenous plant species. The most studied symbiotic hemoglobins are the leghemoglobins of nitrogen-fixing legumes where they facilitate oxygen diffusion within root tissues. Nonsymbiotic hemoglobins have been identified in a wide range of legume and nonlegume plants. The highest expression levels for nonsymbiotic plant hemoglobin are observed in metabolically active or stressed tissue (Anderson C. R., 1996).

Impossible Foods has analyzed globin sequences from various sources, including the soy leghemoglobin protein presented in this notification, as well as widely consumed globin proteins from corn, rice, barley, lupine, horse, tuna, and pig. As detailed in Annex 1, these hemeproteins - animal myoglobins, plant hemoglobins and plant leghemoglobins - are structurally very similar, and all contain the identical heme B cofactor. The abundant consumption of the heme B cofactor is widespread in humans and other animals, as heme proteins, like myoglobins and hemoglobins, are abundant in animal tissues consumed as meat, and also are present in the leaves and other routinely consumed parts of plants. Thus, even though soy leghemoglobin itself is not widely consumed in the human diet, there is overwhelming evidence that heme B-containing globin proteins have been safely consumed throughout human history.

2.5. Specifications for food grade material

LegH Prep, the ingredient used in Impossible Foods's ground beef analogue, is standardized to contain at least six percent (6%) soy leghemoglobin protein. LegH Prep is stabilized with food-grade sodium chloride and sodium ascorbate. The product specification of LegH Prep is presented in Table 1.

Proximate composition and heavy metal composition of LegH Prep were determined by Silliker Inc. (Salida, CA). Impossible Foods measured soy leghemoglobin protein concentration using ultra performance liquid chromatography (UPLC). Soy leghemoglobin protein purity was measured by Impossible Foods using SDS-PAGE, coomassie staining, and gel densitometry. Impossible Foods tested LegH Prep for total aerobic plate counts (AOAC OMA 990.12). AEMTEX Laboratories (Fremont, CA) tested LegH Prep for *Salmonella* (AOAC OMA 2011.03), *Listeria monocytogenes* (AOAC OMA 2010.02), and *E. coli* O157:H7 (AOAC RI 020801).

Five LegH Prep production runs and their respective batch analyses are shown in Table 1. All five batches fall within the specifications outlined in Table 1. Genotoxicology assessments were performed on batch PP-PGM2-16-015-101. To generate a sufficient quantity of material for testing, PP-PGM2-16-015-101 was generated by blending lots PP-PGM2-15-321-101, PP-PGM2-15-341-101, and PP-PGM2-16-004-101. Each of the individual lots that went into the blend conformed to the LegH Prep specifications. Rat systemic toxicology assessments were performed on a freeze-dried sub-lot of PP-PGM2-16-088-101, as freeze-drying was necessary for incorporation of LegH Prep into the animal feed. The relative percent composition of the solid ingredients was consistent between batch PP-PGM2-16-088-101 and PP-PGM2-16-088-301 (the freeze-dried sub-lot).

Table 1. LegH Prep specifications and batch analyses from five independent production runs.

	Specifications	PP-PGM2-16-015-101	PP-PGM2-16-088-101	PP-PGM2-16-102-101	PP-PGM2-16-144-101	PP-PGM2-16-200-101
Soy Leghemoglobin Protein (w/w)[1]	6 – 9%	6.74%	6.39%	6.28%	6.74%	6.95%
Soy Leghemolglobin Protein Purity (w/w)[2]	≥65%	82%	71%	85%	77%	86%
Fat (w/w)	≤2%	0.05%	<0.01%	<0.01%	0.03%	0.08%
Carbohydrates (w/w)	≤4%	1.72%	0.99%	1.67%	2.01%	2.73%
Ash (w/w)	≤4%	1.87%	0.67%	2.63%	2.62%	2.74%
Solids (w/w)[3]	≤24%	14.85%	12.55%	14.92%	17.31%	18.44%
Moisture (w/w)	≥76%	85.15%	87.45%	85.08%	82.69%	81.56%
pH	6.5 – 8.5	7.19	7.19	7.38	7.01	6.77
Lead (ppm)	<0.4	<0.01	<0.01	<0.01	<0.01	<0.01
Arsenic (ppm)	<0.05	0.01	<0.01	<0.01	0.01	<0.01
Mercury (ppm)	<0.05	<0.005	<0.005	<0.005	<0.005	<0.005
Cadmium (ppm)	<0.2	<0.001	<0.001	0.001	0.003	0.001
Aerobic plate count (CFU/g)[4]	<10^4	<10	<10	<10	<10	<10
***E. coli 0157:H7*[5]**	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test
***Salmonella spp.*[6]**	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test
***Listeria monocytogenes*[7]**	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test

[1]Soy leghemoglobin protein may exceed 9% if additional water (moisture) is removed during the concentration step of the manufacturing process. Additional concentration (i.e. less water) does not change the composition of the dry solids.
[2] The balance of the proteins in the preparation is residual *Pichia* proteins.
[3] Percent solids specification is based on the sum of the maximum concentrations of total protein, fat, carbohydrates and ash. Maximum total protein was calculated as the maximum soy leghemoglobin protein concentration divided by the minimum soy leghemoglobin protein purity.
[4] AOAC OMA 990.12
[5] AOAC RI 020801
[6] AOAC OMA 2011.03
[7] AOAC OMA 2010.02
n/a = not applicable

The *Pichia* production organism, MXY0291, does not contain antibiotic resistance genes. Therefore, LegH Prep does not contain antibiotic resistance genes. LegH preparations also do not contain viable MXY0291, the *Pichia pastoris* production organism. The soy leghemoglobin gene (*LGB2*) was generated by DNA synthesis and is the only recombinant DNA within MXY291 that is not native to *Pichia*. Impossible Foods has been able to isolate detectable amounts of *Pichia* DNA from the final heme solution, and it has determined that about 0.2 mg/L of *Pichia* DNA will be present in LegH Prep.

LegH Prep may be stored at -20 °C as a frozen liquid for at least 12 months with no observable change in soy leghemoglobin protein stability or performance in ground beef analogue products.[1]

2.6. Method of Manufacture

LegH Prep is prepared in four stages: construction of the production strain of *Pichia pastoris*, expression of soy leghemoglobin protein in submerged fermentation, enrichment and stabilization of the expressed soy leghemoglobin protein. All materials used in the production of LegH Prep are standard food grade or pharmaceutical grade ingredients or of a purity and quality suitable for their intended use (Aunstrup, Andersen, Falch, & Nielsen, 1979) (Taylor & Baumert, 2013) (Enzyme Technical Association (ETA), 2005) and processing conditions are appropriate for food production under GMP. The product is standardized to a concentration of at least six percent (6%) soy leghemoglobin protein.

2.6.1 Raw Materials

Raw materials used in the fermentation and recovery process for soy leghemoglobin are standard ingredients used in the food/enzyme industry, and follow internal specifications (in line with Foods Chemical Codex, Ninth Edition requirements). These specifications include limits on lead and other pertinent heavy metals. The raw materials are of a purity and quality suitable for their intended use (Aunstrup, Andersen, Falch, & Nielsen, 1979); they are food grade and GRAS, or high-quality chemical or pharmaceutical grades (USP, NF, or ACS grades) from approved suppliers.

2.6.2. Fermentation

Soy leghemoglobin protein is expressed during submerged fed-batch fermentation using the *P. pastoris* MXY0291 production strain described above. Frozen cell banks for the production organism MXY0291 are maintained at -80 °C in 20% v/v glycerol as the source inoculum for soy leghemoglobin production. The master cell bank is stored at multiple locations. Working cell banks are prepared from the master cell bank and are tested for microbial purity, specific growth rate, and soy leghemoglobin yield prior to production fermentation. Fermentation broth is periodically analyzed microscopically to ensure culture purity. Process parameters including pH, temperature, agitation, dissolved oxygen, methanol concentration and glycerol concentration are routinely monitored throughout fermentation. Fermentations that incur microbial contamination and/or other process deviations that affect safety and/or quality are sterilized by steam in place and discarded.

2.6.3 Recovery Process

The *P. pastoris* cells in the fermentation broth are lysed by bead mill mechanical shearing. Insoluble material within the lysate is removed by centrifugation and microfiltration.

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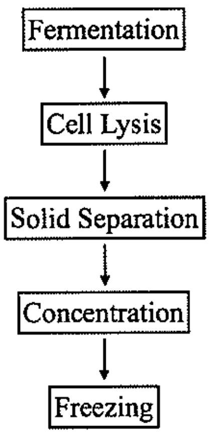
[1] Soy leghemoglobin is stable within Impossible Foods vacuum packed ground beef analogue product for at least 30 days at 4 °C and at least 95 days at -20 °C.

Ultrafiltration is used to concentrate soy leghemoglobin protein. The resulting concentrated sample is formulated with sodium chloride and sodium ascorbate and stored as a frozen liquid. A schematic overview of the manufacturing process is presented in Figure 1.

Figure 1. Schematic overview of the manufacturing process for LegH Prep: fermentation, cell lysis, solid separation, concentration and freezing.



Impossible Foods tests each independent fermentation broth to ensure the absence of *Salmonella* AOAC OMA 2011.03, *Listeria monocytogenes* AOAC OMA 2010.02, and *E. coli* O157:H7 AOAC RI 020801. The final product from every LegH Prep production run is tested for total aerobic plate count AOAC OMA 990.12 and *Salmonella*, *Listeria monocytogenes*, and *E. coli* O157:H7 as described above. The presence of a pathogen, $>10^4$ CFU/g aerobic count, or failure to comply with the specifications outlined in section 3.2 Table 3, would result in the batch being discarded, the execution of additional sanitization standard operating procedures (SSOPs) in compliance with Impossible Foods' internal food-safety standards, and a root cause analysis.

2.7. Strain Construction

2.7.1 Production Strain

Production strain *Pichia pastoris* MXY0291 was constructed from recipient strain Bg11 (MXY0051) using a series of transformations with different expression constructs, in order to express soy leghemoglobin protein. In addition to the protein coding sequence for soy leghemoglobin, MXY0291 contains extra copies of native *Pichia pastoris* heme biosynthetic enzymes and modified *Pichia pastoris* transcription factor Mxr1, all expressed under the strong native *Pichia pastoris* alcohol oxidase promoter (*pAOX1*). This promoter has been demonstrated to produce high levels of recombinant proteins after producing biomass on glycerol, and inducing *pAOX1* with methanol (Cereghino & Cregg, 2000). The genome of MXY0291 is fully sequenced and well-characterized.

The *Pichia pastoris* production strain background complies with the Organization for Economic Development (OECD) criteria for Good Industrial Large Scale Practice (GILSP) microorganisms (OECD, 1992; OECD, 1993). It also meets the criteria for a safe production microorganism as described by Pariza and Foster, Pariza and Johnson, and several expert groups

(EU Scientific Committee for Food, 1992) (FAO/WHO, 1996) (International Food Biotechnology Council, 1990) (Jonas, et al., 1996) (OEDC, 1993) (Pariza, M.W. et al., 1983) (Pariza, M.W. et al., 2001).

2.7.2 Recipient Strain

The recipient strain is *Pichia pastoris* Bg11 (MXY0051), which in turn is a derivative of Bg10. Both strains are commercially available and were purchased from BioGrammatics, Inc. (Carlsbad, CA). BioGrammatics, Inc. describes the lineage of their commercially available Bg10 and Bg11 *Pichia pastoris* strains as follows:[2]

The general taxonomy of *P. pastoris* is:

Name: *Pichia pastoris*
Kingdom: Fungi
Phylum: Ascomycota
Class: Hemiascomycetes
Order: Saccharomycetales
Family: Endomycetaceae
Genus: Pichia
Species: pastoris

The recipient *Pichia pastoris* strain Bg11 was derived from the well-characterized strain Y-11430, which is deposited in the collection at the Northern Regional Research Laboratories (NRRL). The lineage *of P. pastoris* strain NRRL Y-11430 is detailed below, and was previously included in GRN 204, reviewed by the Agency in 2006.

According to the definitive source of yeast taxonomy (Rij, 1984), as well as a thorough literature search, there are no indications that *P. pastoris* has been associated with animal or human illness. The following lineage for the *P. pastoris* Bg10 strain is based on genomic sequencing, literature sources, and from discussions with experts in this area.

The first *P. pastoris* strains were isolated from an oak tree and a chestnut tree and were deposited in the collection at the Northern Regional Research Laboratories (NRRL)[3] (see Figure 2, and www.biogrammatics.com). Yeast strains screened by Phillips Petroleum for growth on methanol included two *P. pastoris* strains, designated NRRL Y-1603 (ATCC accession 28485) (ATCC, 2006b) and NRRL YB-4290 (NCAUR, 2006). Phillips Petroleum identified a *P. pastoris* strain with improved growth characteristics. The strain was designated 21-1 and deposited at NRRL, as NRRL Y-11430 (Wegner, E.H., 1986). This strain is now available from ATCC as 76273 (ATCC, 2005). No records are available confirming that NRRL Y-1603 or NRRL YB-4290 is the progenitor of NRRL Y-11430, but it seems likely that one of them is the progenitor strain (Madden, K.R., 2014). NRRL Y-11430 was the progenitor strain for GS115, a

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[2] Biogrammatics, Inc. supplied this information and the four paragraphs that follow to describe the recipient strain lineage.

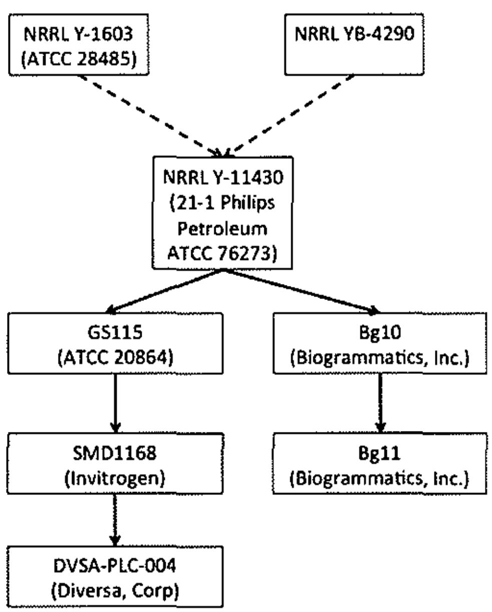
[3] The NRRL collection is now known as the Agriculture Research Service Culture Collection and is at the Microbial Genomics and Bioprocessing Research Unit (MGB) of the National Center for Agricultural Utilization Research (NCAUR) in Peoria, IL.

histidine auxotrophic mutant (his4-) (ATCC, 2006a; (Cregg, 1985)), a common *Pichia pastoris* strain provided in commercial kits by Invitrogen Corporation, and widely used as the parental strain of many biotechnology products. Additionally, the GS115-derived strain SMD1168 is used for the GRAS approved production of BD16449 Phospholipase C (GRN 204). Like GS115, the BioGrammatics, Inc. strain, Bg10 is also a derivative of NRRL Y-11430, and genomic sequencing data performed by BioGrammatics, Inc. confirm the similarity of NRRL Y-11430, Bg10 and GS115 (Figure 2). Additional taxonomic history of these strains is available in a 2009 manuscript by C. Kurtzman (Kurtzman, 2009) and on the Biogrammatics webpage (biogrammatics.com).

BioGrammatics, Inc. further developed the NRRL-Y-11430 strain to remove the native *P. pastoris* plasmids. PCR primers unique to the plasmids were used to screen multiple single-colony isolates for the presence of the plasmids. One isolate without plasmids was selected to become the wild-type (wt) BioGrammatics strain, Bg10. Genomic sequence from Bg10 indicates the plasmids are no longer present, and, benchmarks the similarity of Bg10 with NRRL-Y11430, as well as with GS115. Like NRRL Y-11430 and GS115, Bg10 does not contain antibiotic-resistance genes.

P. pastoris is a methyltrophic yeast that is capable of using methanol as sole carbon source. Alcohol oxidase 1 (Aox1) is the primary enzyme responsible for methanol metabolism, and strains lacking this enzyme have a reduced rate of methanol utilization and are therefore preferred in industrial fermentations due to decreased heat generation and rate of oxygen consumption. Biogrammatics, Inc. deleted the gene encoding for Aox1 from Bg10 using homologous recombination to generate a strain that grows more slowly on methanol-containing induction media. The antibiotic resistance gene and background vector sequences used during homologous recombination were subsequently removed to generate a clean, antibiotic resistance gene-free Bg11 strain, which was purchased by Impossible Foods (Figure 2).

Figure 2. Strain lineage of recipient strain Bg11 (MXY0051)

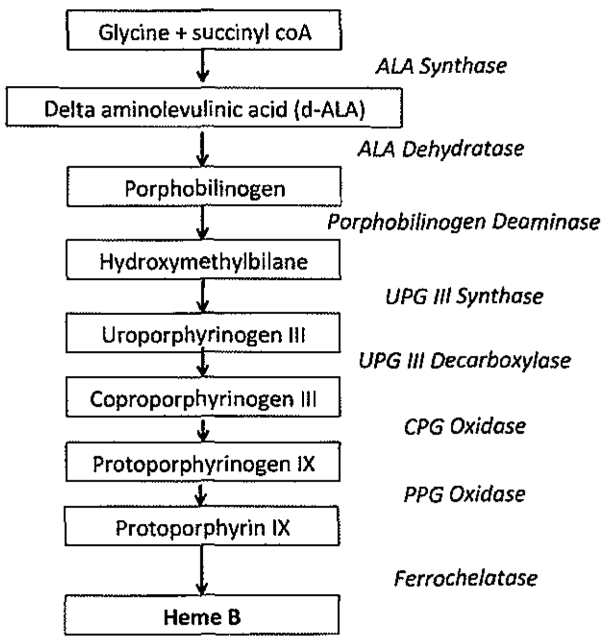


2.7.3 Construction of the Production Strain

2.7.3.1 Construction of MXY0213: Strain Overexpressing the Heme Biosynthesis Pathway

In order to increase the intracellular concentration of heme to generate sufficient heme-bound soy leghemoglobin protein, the heme biosynthetic pathway of Bg11 was up regulated. Heme biosynthesis is the result of an 8-step pathway, each catalyzed by a distinct, highly conserved enzyme (Figure 3).

Figure 3: The highly conserved heme biosynthesis pathway. The enzymes catalyzing each step are shown on the right in italics.



Genes encoding all 8 enzymes of the *Pichia* heme biosynthesis pathway were amplified from the *Pichia* genome and cloned into two plasmids, *pMX349* and *pMX346*. The two plasmids were linearized using restriction enzyme (Pme1) digestion and sequentially transformed into the recipient strain Bg11 leading to integration of the entire cassette expressing the sets of heme enzymes in the genome. Following each round of transformation, the antibiotic resistance gene was removed from the strain. This resulted in MXY0213, a stable strain that contained extra copies of the native *Pichia* heme biosynthesis enzymes under extra copies of the native *pAOX1* promoter.

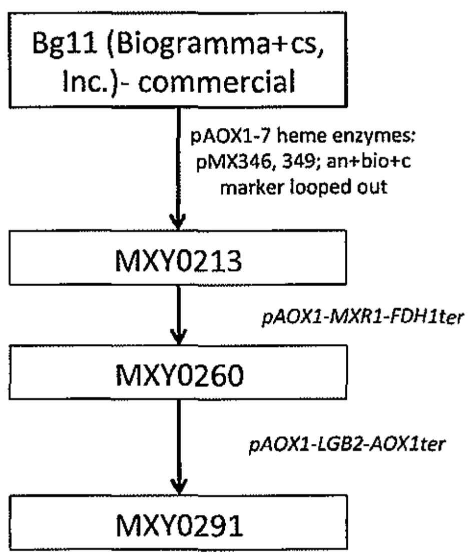
2.7.3.2 Construction of MXY0260: Strain Overexpressing Mxr1 and the Heme Biosynthesis Pathway

Mxr1 is a transcriptional activator of the *pAOX1* promoter. The presence of Mxr1 leads to improved production of the recombinant protein leghemoglobin. A linear cassette of DNA containing modified *Pichia pastoris MXR1* gene under the control of *pAOX1* promoter and *FDH1* terminator (*FDH1ter*) was introduced into MXY0213 by co-transformation. Due to the cloning strategy, the overexpressed Mxr1 protein contains 6 extra amino acids on its N-terminus compared to the native *Pichia pastoris* Mxr1. Mass spectrometry analysis demonstrates that neither the modified Mxr1 protein nor the native Mxr1 protein is detectable in LegH Prep final product. The *pAOX1-MXR1-FDH1ter* DNA cassette and an empty vector containing an antibiotic resistance gene were co-transformed into MXY0213. This enabled selection of transformants containing the empty vector, which were then screened by colony PCR for integration of the cassette at the *pAOX1* locus. Transformants containing the desired *MXR1* integration were subsequently cured of the empty vector by screening for antibiotic sensitivity. Loss of the empty vector was confirmed by PCR. The resulting strain was MXY0260, the parent to the production strain MXY0291.

2.7.3.4 Construction of MXY0291: Production Strain Overexpressing Soy Leghemoglobin

The protein coding sequence from *Glycine max* leghemoglobin *LGB2* was synthesized and codon-optimized for expression in *Pichia pastoris.* A linear cassette of *pAOX1-LGB2-AOX1ter* was PCR amplified and introduced into MXY0260 by co-transformation as described above. qPCR and protein expression assays identified the production strain, MXY0291, which contains 16 copies of the recombinant *LGB2* gene (Figure 4). As described above, antibiotic selection and PCR were used to demonstrate absence of plasmid following co-transformation.

Figure 4. Construction of production strain using recipient strain Bg11 (MXY0051)



2.7.4 Genome Sequence of the Production Strain

The genome of production strain MXY0291 has been completely sequenced and confirmed to contain the following sequences in addition to the background *Pichia pastoris* DNA.

- 16 copies of *pAOX1-LGB2-AOX1ter*
- 1 copy of *pAOX1-MXR1-FDHter*
- 1 copy of a portion of *pMX349* (no antibiotic resistance genes, no origin of replication)
- 2-3 copies of a portion of *pMX346* (no antibiotic resistance genes, no origin of replication)

2.7.5 Stability of the Production Strain

All changes introduced into production strain MXY0291 are stably integrated in the genome and confirmed to be present after > 150-200 generations of growth on non-selective growth media. No plasmid sequences are present in the production strain. Hence, the plasmid sequences will not be transferred from the production strain to a non-related organism.

2.7.6 Absence of Antibiotic Resistance Genes

The production strain MXY0291 does not contain antibiotic resistance genes.

2.7.7 Absence of the MXY0291 Production Organism in the Final Product

The MXY0291 production organism is not detected in LegH Prep in accordance with the recommendations for safety evaluation by the International Food Biotechnology Committee (Coulston and Kolbye, 1990).

2.8. Potential Toxicants

The LegH Prep production strain and manufacturing process do not produce any known toxicants.

PART 3: DIETARY EXPOSURE

3.1 Estimated Dietary Intake

LegH Prep will be marketed for use in ground beef analogue products that provide consumers a flavorful and nutritious alternative to ground beef containing products. Therefore, Impossible Foods has estimated daily intakes of soy leghemoglobin protein by assuming consumers will substitute the ground beef analogue product for the traditional meat product on a 1-for-1 basis. The ground beef analogue will constitute not more than 0.8% soy leghemoglobin protein of the total composition. The use of soy leghemoglobin protein in ground beef analogue products is largely self-limiting based on unacceptable organoleptic properties at levels well above the recommended use level of not more than 0.8% soy leghemoglobin protein of the total composition.

As the highest use case, Impossible Foods has assumed it will capture 100% of the total ground beef market with soy leghemoglobin protein-containing meat analogue products. One hundred percent (100%) of the total meat market represents approximately 500 times the volume of the current meat analogue market size, based on sales estimates.[4]

The Estimated Daily Intake (EDI) of soy leghemoglobin in the target ground beef analogue applications was established using beef consumption data from the National Health and Nutrition Examination Survey (NHANES), conducted in 2007-08 (as published by Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). Because the intended use of LegH Prep is limited to ground beef analogue products, the per capita beef consumption data was multiplied by the percentage of beef that is sold as ground beef, which is 42%, to estimate consumption for this intended use.[5]

3.1.1 EDI for Soy Leghemoglobin Protein

The mean daily consumption of all types of beef is 59 grams for males and females ages 2 and older (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). For ground beef, the mean consumption is 25 grams (59 grams x 42%). Using a conservative approach, Impossible Foods assumes capturing 100% of the ground beef market.

The ground beef analogue product will not contain more than 0.8% soy leghemoglobin protein by mass. This equates to a maximum EDI of 200 mg/person/day of soy leghemoglobin (25 ground beef grams/person/day x 100% market x 0.8% soy leghemoglobin). However, Impossible Foods anticipates the soy leghemoglobin protein to constitute, on average, 0.6% of the ground beef analogue product by mass. This results in an estimated typical daily intake of 150 mg/person/day. These results are presented below in Table 2.

[4] Datamonitor estimates the US meat analogue volume was 53M kg in 2009. USDA-FAS Livestock and Poultry Report, April 2014 estimates 2014 US consumption of 11B kg beef, 8.5B kg pork, and 14B kg broilers. Therefore, the current meat analogue market is less than 0.2% of the overall meat market and capturing 100% of the meat market represents 500 times the current meat analogue market in the US.

[5] http://usda.mannlib.cornell.edu/usda/ers/LDP-M/2000s/2005/LDP-M-10-07-2005_Special_Report.pdf

Table 2. Estimated daily intake of soy leghemoglobin protein

Food Category to be Replaced	Consumer Age (years)	Mean Consumption Ground Beef (g/day)	Anticipated Market Share Replacement (%)	Typical Use Rate (%)*	Soy Leghemoglobin Estimated Typical Daily Intake (mg/person/day)	Max Use Rate (%)*	Soy Leghemoglobin Estimated Maximum Daily Intake (mg/person/day)	Soy Leghemoglobin 90th Percentile EDI (mg/kg/day)
Ground Beef	2 and over	25	100	0.6	150	0.8	200	6.67

* Use rate is percent soy leghemoglobin protein in the ground beef analogue product by mass.

3.1.2 EDI for LegH Prep (dry solids)

While soy leghemoglobin protein is the characterizing component of the LegH Prep, it is the LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components) that is added to the ground beef analogue product. Therefore, an EDI was also calculated for the LegH Prep. Due to the high water content (≥76%) of the LegH Prep, the EDI was calculated based on LegH Prep dry solids (*see* Table 1).

The EDI for LegH Prep dry solids was calculated as follows: The typical and maximum EDIs for the soy leghemoglobin protein were divided by 9% (which represents the maximum amount of soy leghemoglobin protein within LegH Prep, *see* Table 1). This represents the typical and maximum EDI for LegH Prep (liquid formulation). To obtain the EDI for the LegH Prep dry solids, the liquid formulation EDI was multiplied by 24% (which the maximum percent solids within LegH Prep, *see* Table 1). For example, the typical use EDI for LegH Prep dry solids was calculated as:

(150 mg/person/day soy leghemoglobin protein) ÷ (9% maximum soy leghemoglobin protein within LegH Prep) x (24% maximum solids within LegH Prep) = 400 mg/person/day LegH Prep dry solids.

The estimated maximum daily intake for LegH Prep dry solids was calculated using the same equation with 200 mg/person/day soy leghemoglobin protein (assuming a 0.8% use rate). The results are presented in Table 3.

Table 3. Estimated daily intake of LegH Prep (dry solids)

Food Category to be Replaced	Consumer Age (years)	Mean Consumption Ground Beef (g/day)	Anticipated Market Share Replacement (%)	Typical Use Rate (%)*	LegH Prep Dry Solids Estimated Typical Daily Intake (mg/person/day)	Max Use Rate (%)*	LegH Prep Dry Solids Estimated Maximum Daily Intake (mg/person/day)
Ground Beef	2 and over	25	100	0.6	400	0.8	533

* Use rate is percent soy leghemoglobin protein in the ground beef analogue product by mass.

3.2. Estimation of the 90th Percentile Intake for Soy Leghemoglobin Protein

Following the FDA's "Guidance for Industry: Estimating Dietary Intake of Substances in Food"[6] to estimate daily intake values, the pseudo 90th percentile for soy leghemoglobin protein consumption would be 2 times the mean EDI. The maximum mean EDI is 200 mg soy leghemoglobin/person/day at the maximum anticipated use rate (0.8%). Therefore, the exposure to high users (90th percentile) will be approximately 400 mg soy leghemoglobin /person/day if soy leghemoglobin protein is used at the maximum anticipated rate (0.8%).

For the basis of safety testing, the 90th percentile consumption of soy leghemoglobin was calculated using 25 grams ground beef/person/day x 0.8% soy leghemoglobin/ground beef / 60 kg/person x 2. Therefore, the 90th percentile consumption equates to 6.67 mg/kg/day, which was used as the basis for safety testing.

Impossible's products, formulated with soy leghemoglobin, deliver approximately the same amount of heme protein as is found in beef. Therefore, if consumers substitute Impossible's ground beef analogue for conventional beef, overall consumption of heme proteins is approximately the same.

It is important to note that the vast majority of heme proteins consumed in the diet are myoglobins contained in meat and poultry products. For the US population, per capita mean consumption of meat and poultry products is 154 g/person/day (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). Assuming an average myoglobin concentration for meat and poultry products of 0.5% (Yip & Dallman, 1996), the average per capita myoglobin consumption would be 0.77 g/person/day myoglobin and the 90th percentile intake would be 1.54 g/person/day. In contrast, the 90th percentile EDI for soy leghemoglobin is lower, at 0.4 g soy leghemoglobin protein/person/day.

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[6] http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ingredientsadditivesgraspackaging/ucm074725.htm

PART 4: SELF-LIMITING LEVELS OF USE

Use of soy leghemoglobin in ground beef analogue products is self-limiting because use rates that exceed the maximum recommended level of 0.8% soy leghemoglobin protein result in an increasingly unacceptable organoleptic profile.

PART 5: EXPERIENCE BASED ON COMMON EXPERIENCE IN FOOD BEFORE 1958

This section is not applicable to this application.

PART 6: NARRATIVE

6.1 History of Safe Use

6.1.1 Soy

Soy leghemoglobin is derived from the root nodule of the soy plant. While the root nodules are not typically consumed, soy has been part of the human diet for more than 5000 years (Lee, Crawford, Liu, Sasaki, & Chen, 2011). The safety of soy proteins found in the soybean is well established (Riaz, 2006). In the 2010 marketing year, 249 million metric tons of soybeans were produced worldwide (Food and Agricultural Organization of the United Nations, 2010). Although the majority of the crop is used for animal feed, approximately 14% is used for human food in the form of traditional soy foods, such as tofu, soymilk, natto, miso, and bean sprouts. Soy protein ingredients are also used to formulate a wide range of food products, including infant formula, dairy and meat alternatives, nutritional supplements and energy bars (Golbitz & Jordan, 2006). The use of soy proteins is widely accepted in the United States. The FDA has affirmed the safety of soy protein isolates for inclusion in many products (GRN 134, GRN 186, and GRN 283), and has approved a health claim for consumption of soy protein reducing the risk of coronary heart disease (21 CFR 101.82). In 2000, the U.S. Department of Agriculture (USDA) issued a ruling allowing soy protein to completely replace animal protein in the National School Lunch Program (Messina, 2006). Thus, the safety of soybeans in human food has been clearly demonstrated and its use reviewed extensively by United States regulatory agencies.

6.1.2 Soy Leghemoglobin

Heme proteins are found in most organisms, including bacteria, protozoa, fungi, plants and animals (Everse, 2004) (Hardison, 1998) (Wajcman & Kiger, 2002). Soy has been shown to express three hemoglobin proteins: symbiotic, nonsymbiotic and truncated (Lee, Kim, & An, 2004). The proteins share a common evolutionary origin (Vinogradov et al. 2007) and, based on structural studies and homology modeling, share a common three-dimensional structure involving an alpha helical globin-fold wrapped around a heme B molecule (Ellis et al. 1997) (Annex 1). The members of this protein family are all involved in selective transport, storage or buffering of oxygen levels in cells and tissues (Vinogradov and Moens 2008). The shared and well-characterized physiology of these proteins strongly supports the inference that the shared three-dimensional structure of these globin proteins evolved to bind oxygen.

Symbiotic hemoglobins, found predominately in legume species, function in the nitrogen fixation process in concert with the bacterium Rhizobium where they facilitate oxygen diffusion within host tissues. Symbiotic plant hemoglobins, which evolved from non-symbiotic hemoglobins (Gupta, 2011) (Wajcman & Kiger, 2002), are commonly referred to as leghemoglobins. Leghemoglobins' structure and their oxygen binding mechanism are similar to those of animal muscle myoglobin proteins (Hargrove, 1997). The primary sequence of soy leghemoglobin is not homologous to the primary sequences of mammalian myoglobins. However, the primary sequence of soy leghemoglobin does not contain significant homology to any known allergens or toxins, and therefore does not present a known safety concern (see section 6.4.4).

Non-symbiotic plant hemoglobins from soy, barley, rice, corn, and mung beans are widely consumed in the diet. Anderson *et al.* demonstrated that the nonsymbiotic hemoglobin in soy was expressed in various plant tissues including stems, shoots, cotyledon, leaves, and root hair (Anderson C. R., 1996). These soy tissues are commonly consumed in the diet in the form of soybean sprouts. Sprouted barley, which is widely used in the beverage industry (malted barley) and in the baking industry (malted barley flour), has been shown to express hemoglobin one day after imbibition (Duff, Guy, Xianzhou, Durnin, & Hill, 1998). Non-symbiotic hemoglobins are expressed in the rice embryo as well as in the coleoptiles and seminal root of sprouted rice, which is consumed as part of the diet as well (Lira-Ruan, Ruiz-Kubli, & Arredondo-Peter, 2011). Non-symbiotic hemoglobin is expressed in corn seedlings and may provide a good source of bioavailable heme in mature corn seeds (Bodnar, 2011). Impossible Foods has detected non-symbiotic hemoglobin in mung bean sprouts by mass spectrometry. The three dimensional structure of soy leghemoglobin is highly similar to the non-symbiotic hemoglobins of corn, rice, and barley (Annex 1), and although there are no crystal structures for non-symbiotic hemoglobins from soy or mung beans, based on the highly similar structures of non-symbiotic hemoglobins from corn, rice and barley to each other and to soy leghemoglobin, Impossible Foods expects that they (soy and mung) are likewise structurally similar to soy leghemoglobin.

Thus, hemoglobin proteins of plant and animal sources are widely consumed in the human diet, and represent a highly bioavailable source of dietary iron for human nutrition. Proulx and Reddy demonstrated that soy leghemoglobin and bovine hemoglobin showed similar iron bioavailability within a food matrix, both of which were higher than free iron (Proulx & Reddy, 2006). Furthermore, plant-derived hemoglobins are already prevalent in our food system through malted grain products and sprouted seeds, grains, rice and beans (pulses) (Anderson, Jensen, Leewellyn, Dennis, & and Peacock, 1996) (Duff, Guy, Xianzhou, Durnin, & Hill, 1998) (Lira-Ruan, Ruiz-Kubli, & Arredondo-Peter, 2011).

The heme B moiety plays a central role in oxygen binding, and the structure of the globin protein serves to isolate the heme from other molecules by creating a small binding pocket inaccessible to most other molecules (Ellis et al. 1997). Thus, heme B-containing globin proteins remain largely inert so long as the three dimensional structure is maintained. When globin proteins are heated, as in cooking, or exposed to a low pH environment, as in the human stomach, the protein unfolds and the heme B molecule is released (Annex 1). Impossible Foods has shown that heme B, released when myoglobin is heated to cooking temperature, plays a major role in catalyzing the production of the flavors and aromas characteristic of cooked meat. Crucially, however, this catalysis is a function of the heme B molecule, and is independent of the specific protein in which it was bound prior to cooking.

The abundant consumption of heme B is widespread in humans and other animals, as heme proteins are abundant in animal tissues consumed as meat, and are also present in the leaves and other routinely consumed parts of plants. Thus, there is overwhelming evidence that heme B-containing proteins, which are functionally equivalent to soy leghemoglobin presented in this notification, have been safely consumed throughout human history.

There is no evidence that any of the globin subfamily that contains the plant hemoglobins have any biochemical activities other than the binding of oxygen (O_2) or the structurally similar carbon dioxide (CO_2), nitrous oxide (NO), and carbon monoxide (CO). The three-dimensional structure of leghemoglobin contains no additional active sites to distinguish it from widely consumed heme proteins, nor is there any biochemical or physiological evidence that this protein has any enzymatic activity or other function outside of controlled binding to oxygen.

Thus, there is no evidence to suggest that soy leghemoglobin in food will behave any differently from the myriad other functionally equivalent and widely consumed globin proteins in the human diet. However, due to a lack of widespread human consumption, Impossible Foods has used rigorous scientific procedures to evaluate soy leghemoglobin for potential toxicity or allergenicity, with results confirming that LegH Prep is non-toxic and poses negligible risk of allergenicity.

6.1.3 Pichia pastoris

As discussed in greater detail in other sections of this GRAS notification, soy leghemoglobin protein is produced in the well-characterized expression host *Pichia pastoris* (Cereghino & Cregg, 2000). *Pichia* belongs to the same family of yeast (Saccharomycetaceae) as several yeast genera widely used in food: Saccharomyces, Torula, Yarrowia, Dekkera and Brettanomyces. Brettanomyces, a yeast traditionally used in brewing Belgian beers, belongs to the same sub-family of yeast as *Pichia* - the Pichiaceae. Yeast extract (from *S. cerevisiae* and Torula) is frequently directly consumed in substantial quantities in human diets. Impossible Foods' genetically modified *Pichia* production strain complies with the OECD (Organization for Economic Development) criteria for GILSP (Good Industrial Large Scale Practice) microorganisms (OECD, 1992). It also meets the criteria for a safe production microorganism as described by Pariza and Foster, Pariza and Johnson, and several expert groups (Berkowitz & Maryanski, 1989) (EU Scientific Committee for Food, 1992) (FAO/WHO, 1996) (International Food Biotechnology Council, 1990) (Jonas, et al., 1996) (OEDC, 1993) (Pariza, M.W. et al., 1983) (Pariza, M.W. et al., 2001).

The American Association of Feed Control Officials (AAFCO) has approved the *E. coli* enzyme phytase derived from the fermentation of recombinant *Pichia pastoris* for use in animal feed (AAFCO, 2013). *Pichia pastoris* is also the host used for production of nitrate reductase (The Nitrate Elimination Co. Lake Linden, MI), an enzyme used for treatment of potable water. *P. pastoris* is also approved by FDA as an animal feed protein source allowed in broiler feed up to10% of the total feed (FDA 21 CFR Part 573, 1993).

Pichia pastoris does not produce active toxins (Pariza & Johnson, 2001). *Pichia pastoris* has been placed in the Biosafety Level 1 (BSL-1) class by the ATCC organization, indicating *Pichia* is a well-characterized agent not known to cause disease in healthy human adults, and to be of minimal hazard to laboratory personnel and the environment (Center for Disease Control, 1999). Toxicity studies done in support of the above-referenced *P. pastoris*-approved animal feed also demonstrated that *P. pastoris* is neither pathogenic nor toxigenic (FDA 21 CFR Part 573, 1993). Moreover, Impossible Foods commissioned systemic toxicity and genotoxicity testing on LegH Prep to ensure that the residual *Pichia* proteins and cellular components present in LegH Prep are non-toxic.

Impossible Foods' *Pichia pastoris* production strain MXY0291 is derived from a strain lineage with a long history of safe use, as outlined in GRN 204. All genetic modifications made to generate MXY0291 are well-characterized by full genome sequencing and conform to the guidelines for generating safe production strains for the recombinant production of food ingredients (Olempska-Beer, Merker, Ditto, & DiNovi, 2006). LegH Prep does not contain the production organism or antibiotic resistance genes. Impossible Foods has been able to isolate detectable amounts of *Pichia* DNA from the final LegH Prep solution, and it has determined that about 0.2 mg of *Pichia* DNA will be present in about one liter of LegH Prep. Impossible Foods has used mass spectrometry to identify the *Pichia pastoris* proteins that are present in LegH Prep at $\geq$1% of the total protein fraction. As described below, the sequence of each protein was analyzed to ensure that the *Pichia* proteins present in LegH Prep do not contain significant homology to known allergens. All of the identified co-purifying proteins have highly conserved orthologues in yeast species used in food, such as *S. cerevisiae*.

6.1.4 Method of Manufacturing

All materials used in the production of LegH Prep are standard food grade or pharmaceutical grade ingredients used in the food industry. The raw materials are of a purity and quality suitable for their intended use (Aunstrup, Andersen, Falch, & Nielsen, 1979). The process to isolate soy leghemoglobin protein from a well-characterized fermentation medium that complies with the Enzyme Technical Association's guidelines for microbially derived recombinant proteins follows current Good Manufacturing Practices (GMP) (Enzyme Technical Association, 2005) (Taylor & Baumert, 2013). The product is standardized to a concentration of at least six percent (6%) soy leghemoglobin protein. The soy leghemoglobin protein has highly advantageous properties in meat and poultry analogue products, which will provide consumers a nutritious and flavorful alternative to foods derived from animals, with a much-reduced environmental impact.

6.2 Summary of Adverse Findings in the Literature

Impossible Foods is not aware of any studies in the literature indicating that either soy leghemoglobin or *Pichia pastoris* is not safe for the intended use proposed in this GRAS notification.

6.3 Toxicology Studies

6.3.1 Subacute Toxicity

<u>14-Day non-GLP Dietary Toxicity and Palatability Study in Rats (Study 43167)</u>

Impossible Foods commissioned a non-GLP 14-day dietary toxicity/palatability study in rats to assess the feasibility of oral administration of LegH Prep (which contains soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) and to establish the dose range for a subsequent GLP 28-day dietary toxicology study. The study was conducted by Product Safety Labs (Dayton, NJ, USA). The LegH Prep test article was freeze dried; freeze drying allowed for increased test article concentration in the feed and facilitated homogeneous dietary mixing. Doses of 0, 125, 250, and 500 mg soy leghemoglobin/kg bw/day were administered in the diet to CRL Sprague-Dawley CD® IGS rats (6 male, 6 female per group) for 14 days. Experimental observations included clinical observations, food consumption, body weight, hematology, and liver, spleen and bone marrow weight and histopathology. There were no reported treatment-related adverse findings that were statistically different from the controls. Therefore, it was concluded that 500 mg soy leghemoglobin/kg/day would be well-tolerated by rats in a feeding study of longer duration.

6.3.2 Repeated Dose Toxicity

6.3.2.1 28-Day GLP Dietary Toxicity Study in Rats (Study 43166)

Impossible Foods commissioned a GLP 28-day dietary toxicology study in rats to determine the no observed adverse effect level (NOAEL) for LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) (Annex 2). The study was conducted by Product Safety Labs (Dayton, NJ, USA). The study was designed to meet the guidelines in the US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. Subchronic Toxicity Studies with Rodents (2007) and the OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Part 407): Health Effects, Repeated Dose 28-Day Oral Toxicity Study in Rodents (2008). The study was conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987, which is compatible with OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

6.3.2.1.1 Study Details

The LegH Prep test article (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) was freeze-dried lot PP-PGM2-16-088-101, which was given a new sub-lot of PP-PGM2-16-088-301. As in the 14-day dietary study, freeze drying allowed for increased test article concentration in the feed and facilitated homogeneous dietary mixing. Dietary doses of 0, 512, 1024, and 1536 mg/kg/day of freeze dried LegH Prep (LegH Prep solids) were selected to correspond to 250, 500, and 750 mg/kg/day of soy leghemoglobin (Table 4). The maximum dose of 750 mg/kg/day soy leghemoglobin was selected to achieve a concentration greater than 100-fold above the anticipated 90th percentile EDI (section 3.1). A control group received unformulated feed. To maintain target dietary doses throughout the study, concentrations in the test diets were calculated based on the most recent group body weight and food consumption data. The rats were CRL Sprague-Dawley CD® IGS. There were 10 rats per sex per group.

Table 4. Dosing information for groups in 28-day rat feeding study.

Group	Number of Animals per Group (Male/Female)	Target Exposure of Test Substance LegH Prep Dry Solids (mg/kg/day)	Target Exposure of Soy Leghemoglobin (mg/kg/day)
1	10/10	0	0
2	10/10	512	250
3	10/10	1024	500
4	10/10	1536	750

Experimental observations included ophthalmologic evaluations, clinical observations, body weights, food consumption, clinical pathology including blood chemistry, hematology, coagulation, and urinalysis, gross necropsy, organ weights, and histopathology.

6.3.2.1.2 Study Results

There were no mortalities, clinical observations, ophthalmology, body weight, body weight gain, food consumption, or food efficiency changes attributable to LegH Prep administration for either sex. Additionally, there were no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or female rats. Changes in coagulation parameters were limited to a non-dose-dependent increase in activated partial thromboplastin time observed in Group 3 and 4 males which, due to its very slight magnitude and lack of correlating pathological or clinical finding, is considered non adverse.

There were no test substance-related effects reported during necropsy, organ weights, macroscopic observations, or histopathology in the male and female animals, with a single exception of an increased incidence in the metestrus stage of the estrous cycle in groups 2 and 4 (Annex 2). As discussed in detail below, the control animals used in this study, as well as the treated animals, all had distributions of estrus cycle stages that deviated significantly from published reports, suggesting the possibility of a sampling artifact unrelated to the treatment. A follow-up study (section 6.3.2.2) demonstrated that the observed distributions were very likely due to sampling and assessing estrous cycle distribution on a single day, rather using a longitudinal study that would assess the totality of the estrous cycle, and is not indicative of an adverse health effect.

Because of the estrous cycle distributions reported in the control group as well as the test animals in the 43166 study, Impossible Foods elected to carry out a more extensive and rigorous longitudinal study focusing on the effects of the LegH Prep on the estrous cycle of a larger group of female rats. The results of that study, described below, provide strong evidence that the estrous cycle distribution of a group of rats on a given day commonly deviates greatly from their distribution over time, and provides a highly unreliable picture of estrous cycle function.

6.3.2.2 28-Day Investigative Study in Rats with 14-Day Estrous Cycle Pre-Screen (Study 44856)

To directly address the estrous cycle distributions observed in study 43166, Impossible Foods commissioned a non-GLP investigative 28-day dietary study (44856) in rats with a focus on estrous cyclicity (Product Safety Labs, Dayton, NJ, USA) (Annex 3). The study design included a 14-day estrous cycle pre-screen to ensure that only animals with regular cyclicity advanced to the test article-dosing phase. The estrous cycle was monitored daily for the last 14 days of the 28-day dosing period, which is consistent with the OECD 421 guidelines for estrous cycle evaluation. At study termination, the reproductive organs were evaluated macroscopically and microscopically.

6.3.2.2.1 Study Details

The freeze-dried LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) test article from study 43166 was also used in study 44856 (PP-PGM2-16-088-301). Dietary doses of 0, 512, 1024, and 1536 mg/kg/day of freeze dried LegH Prep were selected to correspond to 0, 250, 500, and 750 mg/kg/day of soy leghemoglobin. A control group received unformulated feed. To maintain target dietary dose levels throughout the study, concentrations in the test diets were calculated based on the most recent group body weight and food consumption data. There were 15 female CRL Sprague-Dawley CD® IGS per group.

Prior to the 28-day dosing phase, estrous was determined daily for 14 days, by vaginal lavage, to ensure that each animal had an average estrus cycle length that was consistent with published literature. Estrous was also determined daily for the last 14 days of the 28-day dosing period to detect any changes in average estrous cycle length as a result of LegH Prep consumption. By monitoring the estrous cycle over time in each rat, the study avoided the sampling artifact of the previous study. The estrus cycle was not monitored for the first 14-days of the dosing period to avoid over-manipulating the animals.

Additional experimental observations included clinical observations, body weights, food consumption, gross necropsy, reproductive organ weights (uterus and ovaries with oviducts), and histopathology on reproductive organs (vagina, cervix, uterus, ovaries, and oviducts).

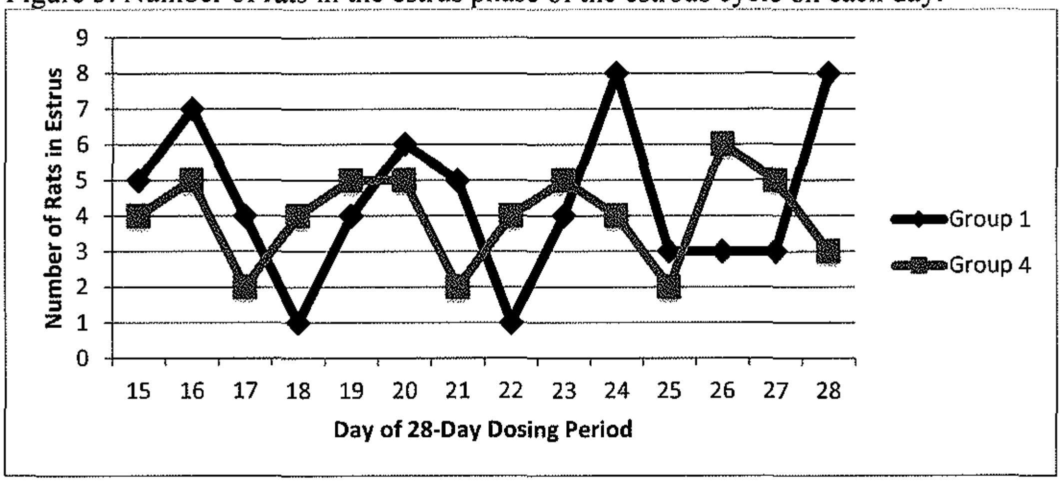
6.3.2.2.2 Study Results

During the 14-day pre-dosing period, there was no significant change in average estrous cycle length between groups 1 through 4, and all animals showed regular estrous cyclicity. Therefore, all animals were advanced to the 28-day dosing phase. During the dosing phase, there were no clinical observations attributable to the administration of LegH Prep. There were no changes in body weight, rate of body weight gain, food consumption, and food efficiency attributable to LegH Prep administration. Mean number of estrus cycles for female rats in groups 2-4 were comparable to control group 1 throughout the study. There were no macroscopic and microscopic observations or organ weight changes attributed to the LegH Prep administration. Therefore, under the conditions of this study and based on the toxicological endpoints evaluated, administration of LegH prep at doses up to 1536 mg/kg/day total dry solids or 750 mg/kg/day of active ingredient (soy leghemoglobin) did not cause any effect in estrus cyclicity or reproductive organ pathology of female Sprague Dawley rats.

The results from study 44856 fully address the potential concerns raised by study 43166, and demonstrate that LegH Prep does not affect the female rat estrous cycle. Each point is discussed below in greater detail.

Despite intrinsically normal estrous cycles, the distribution of estrous cycle stages on any given day can often be extremely deviant from the within-rat distribution over time (Figure 5). Indeed, had the animals been analyzed by necropsy on day 18 of the dosing period, one would have drawn a completely different conclusion regarding the test article effect on estrous cycle than had the necropsy been performed on day 21. Thus, to avoid sampling artifacts, proper evaluation of the effect of a test substance on the estrous cycle requires an extended longitudinal observation as performed in study 44856, in which no test article-dependent effect on the female estrous cycle length or progression was reported.

Figure 5. Number of rats in the estrus phase of the estrous cycle on each day.



There was no difference in mean number of estrous cycles between groups in either the pre-dosing or dosing phase of the study. All animals showed estrous cyclicity that was consistent with published literature (Westwood, 2008). The daily estrous cycle monitoring that was performed in study 44856 follows OECD 421 guidelines, and demonstrates that all groups were cycling normally as expected based on published literature (Westwood, 2008).

Study 43166 showed a decrease in uterine weights that corresponded to a decreased incidence of fluid filled uteri in group 2 and 4 females. In study 44856, there was no significant difference in organ weights for the uterus or ovaries with oviducts between groups 1 through 4. Moreover, the presence of fluid filled uteri did not differ across groups (Table 5). Published literature demonstrates that the presence of fluid filled uteri and uterine weight correlates with estrous cycle stage (Westwood, 2008). Our results from study 44856 reveal a similarly consistent correlation. Thus, the simplest explanation for the decrease in uterine weights observed for groups 2 and 4 in study 43166 is that the animals within those groups had a different distribution of estrous cycle stages that typically correspond to lower uterine weight in healthy rats, compared with groups 1 and 3.

Table 5. Study 44856 summary of necropsy observations in the uterus.

	Group 1 0 mg/kg/day Soy Leghemoglobin N=15	**Group 2 250 mg/kg/day Soy Leghemoglobin N=15**	**Group 3 500 mg/kg/day Soy Leghemoglobin N=15**	**Group 4 750 mg/kg/day Soy Leghemoglobin N=15**
Number of uteri submitted for examination	13	14	15	15
Fluid filled	2	1	1	2

In study 44856, Impossible Foods commissioned Karen Regan, DVM, DACVP, DABT (Regan Path/Tox Services, Inc., Ashland, OH, USA) for histological evaluation of the female reproductive organs. Dr. Regan has extensive experience in the evaluation of rat reproductive systems, and currently serves as FDA advisory committee member for reproductive toxicology. Prior to finalizing the pathology report, Impossible Foods shared the draft report for study 43166 with Dr. Regan to ensure that she would look for the potential effects noted in that study.

In study 44856, Dr. Regan performed a blind estrous cycle determination as well as a histological assessment on the vagina, uterus, ovaries, oviducts, and cervix of the control (group 1) and high dose (group 4) animals. Dr. Regan concluded that there were no test article-related microscopic observations in the reproductive tissues examined. All animals were considered to be cycling normally, with the exception of a single control animal that appeared to have a prolonged estrus based on the morphology of the ovaries and uterus. This control animal finding was considered to be spontaneous and incidental because of the lack of similar findings in animals at the higher dose levels. Within groups 1 and 4, all animals had evidence of old and recent corpora lutea and follicles at various stages of development in the ovaries, and had reproductive tissue morphology consistent with the stage of the cycle they were in. One Group 2 animal had prolonged estrus based on morphology of the ovaries, including large atretic follicles, multiple corpus lutea at a similar state of atresia, and presence of squamous metaplasia of the uterus. These findings were considered spontaneous and incidental due to the lack of similar findings at higher dose levels. One control animal had large atretic follicles observed in both ovaries, and one group 4 animal had lutenized follicles (follicles with evidence of lutenization in the wall but have not ovulated) in both ovaries. Both of these observations are reported as background findings in rats of the strain and age used in this study (Dixon et al. 2014) and were considered incidental because of their singular occurrences.

In summary, in study 44856, Dr. Regan and Product Safety Labs concluded that there was no test substance-related effect on reproductive macroscopic or microscopic observations, reproductive organ weights, or estrous cyclicity.

6.3.2.3. Pathology Peer Review on 28-Day GLP Dietary Toxicity Study in Rats (Study 43166)

Because no test article-related effects on the female estrous cycle were seen in study 44856, Impossible Foods commissioned a pathology peer review on the reproductive organs from study 43166. Dr. Regan served as the review pathologist. The review pathologist received and evaluated histological slides for the cervix, ovaries, oviducts, uterus and vagina, along with the corresponding macroscopic and microscopic finding noted by the study pathologist. Both the study pathologist and review pathologist met and performed an in-person slide review in June 2017, and reached a consensus evaluation that is reflected in the pathology report for study 43166. Both pathologists were in agreement on the estrous cycle staging; however, the presence of old and recent corpora lutea suggests that the animals were cycling normally. Moreover, study 44856 clearly illustrates that that there is no test article-dependent effect on estrous cyclicity. In summary, although the study pathologist for study 43166 initially reported a possible change in the estrous cycle, following peer review, a consensus was reached that there were no test article-dependent effects on the female estrous cycle and reproductive organs.

6.3.2.4. NOAEL

In the 28-Day GLP Dietary Toxicity Study in Rats (Study 43166), there were no test article-related adverse effects observed in the male or female animals at the maximum dose tested. Therefore, the no observed adverse effect level (NOAEL) for administration of LegH Prep solids in the diet of male and female Sprague Dawley rats was the maximum dose tested, 1536 mg/kg/day, which corresponds to 750 mg/kg/day of the active ingredient soy leghemoglobin. The Acceptable Daily Intake (ADI) is determined by dividing the NOAEL by an acceptable Uncertainty Factor; 100-fold is generally accepted.[7] The ADI for soy leghemoglobin is 750/100 or 7.5 mg/kg/day. The 90th percentile EDI for soy leghemoglobin is 6.67 mg/kg/day. Since the EDI is lower than the ADI, these results suggest there are no safety concerns.[8]

6.3.3 Mutagenicity/Genotoxicity Studies

To evaluate the potential genotoxic activity of LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1), Impossible Foods commissioned a bacterial reverse mutation assay performed by Product Safety Labs (Dayton, NJ, USA) and an *in vitro* mammalian chromosome aberration test in human lymphocytes performed by Eurofins (Munich, Germany). Both studies were conducted consistent with OECD Principles of Good Laboratory Practice (as revised in 1997) and OECD Testing Guidelines for test 471 (reverse mutation) and test 473 (chromosomal aberration). The test article for both studies was batch PP-PGM2-16-

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[7] The food additive regulations recommend a safety factor of 100, in the absence of extenuating circumstances. 21 C.F.R. 170.22.

[8] FDA. Chapter II: Agency Review of Toxicology Information in Petitions for Direct Food Additives and Color Additives Used in Food. Available at: https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/UCM078724.pdf

015-101. These studies used the standard liquid formulation of LegH Prep since, unlike the animal feeding studies, freeze drying was not required for test article administration. Reports for each study are located in Annexes 4 and 5.

6.3.3.1 Bacterial Reverse Mutation Assay

The bacterial reverse mutation (Ames) test evaluated the potential for LegH Prep to induce gene mutations in bacteria (Annex 4). Point mutations which involve substitution, addition or deletion of one or a few DNA base pairs were measured in amino acid-requiring strains of *Salmonella typhimurium* (*S. typhimurium*, ST) and *Escherichia coli* (*E. coli*, EC) by their ability to functionally reverse mutations. These reverse mutations resulted in revertant colonies of bacteria with restored capability to synthesize the essential amino acid. The bacterial strains evaluated were *S. typhimurium* TA1535, TA1537, TA98, TA100, and *E. coli* WP2 uvrA. LegH Prep was tested up to a maximum concentration of 74,000 µg/plate, which corresponded to a maximum soy leghemoglobin concentration of 5,000 µg/plate. Eight dose levels without precipitation, toxicity or plate contamination were evaluated for all strains; therefore bacterial mutagenicity was adequately assessed. The main test was conducted using the plate incorporation method in both the absence and presence of metabolic activation (chemically-induced rat liver S9 mix). The results of the test were confirmed using a similar study design, but employing the pre-incubation modification of the Ames test. No signs of precipitation or contamination were reported in any of the strains. No signs of toxicity were reported in any strains in either plate incorporation or pre-incubation method in presence or absence of S9. In conclusion, based on these findings and on the evaluation system used, LegH Prep possesses no mutagenic activity in the Ames assay.

6.3.3.2 *In Vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes

A chromosome aberration assay was carried out in order to investigate a possible potential of soy leghemoglobin and the LegH Prep to induce structural chromosome aberrations in human lymphocytes (Annex 5). The metaphases were prepared 24 hours after start of treatment with the test item. The treatment interval was 4 hours without and with metabolic activation (Experiment I) and 24 hours without metabolic activation (Experiment II). Duplicate cultures were set up. Per culture, 150 metaphases were scored for structural chromosomal aberrations.

The following soy leghemoglobin concentrations were evaluated. Experiment I: 500, 1000, 2500 and 5000 µg/mL soy leghemoglobin; Experiment II: 100, 200, 500 and 1000 µg/mL soy leghemoglobin. In Experiment II, precipitation occurred at concentrations 500 µg/mL and higher during the fixation of the cells. In contrast to Experiment I, in the experiment with long-term treatment, the test item was not removed by repeated washing steps, as the treatment period is stopped by the fixation step directly. When the cells were spread on the object slides, the precipitation appeared as a greenish lacquer coat, visible by eye and with the aid of an inverted microscope. The evaluation of aberration rates was not affected.

In each experiment, percent relative mitotic index was measured for each soy leghemoglobin concentration. A relative mitotic index greater than 45% is required to accurately measure chromosome aberrations. In Experiment I without metabolic activation, the decrease below 70% relative mitotic index was seen at concentrations of 1000 µg/mL (69%), 2500 µg/mL (56%) and 5000 µg/mL (54%) (Annex 5, *see* Table 5). In Experiment I with metabolic activation no decrease below 70% relative mitotic index was observed. As noted by the OECD guidelines, mitotic index is an indirect measurement of toxicity that can be influenced by a number of factors such as time and cell cycle disruption, and additional data such as cell cycle delay is often helpful in assessing toxicity.[9] In the current experiments, cell cycle delay was assessed in the cell proliferation using the BrdU technique. No biologically significant decrease in proliferation was noted in Experiment I, and the levels of the mitotic index remained above the 45% required to accurately assess chromosomal aberrations. Further, as the report in Annex 5 notes, the cytotoxicity is likely even lower than shown in Experiment I without metabolic activation, as there appeared to be a detoxification in the Experiment I with metabolic activation.

In Experiment II without metabolic activation, cytotoxic effects regarding the mitotic index were reported at concentrations of 500 µg/mL (69%), 1000 µg/mL (53%), 2000 µg/mL (26%), 3000 µg/mL (13%), 4000 µg/mL (38%) and 5000 µg/mL (42%) (Annex 5, *see* Table 7).

In Experiments I and II, no biologically relevant increase in the frequencies of polyploid cells was reported at concentrations up to 5000 µg/mL. In experiment I, no biologically relevant decreases of the proliferation index were reported at concentrations up to 5000 µg/mL. In experiment II, the values of the proliferation index of the negative controls were 1.56. The proliferation index of the 500 and 1000 µg/mL groups were 1.23 and 1.12. Decrease of 79% at 500 µg/mL and 72% at 1000 µg/mL of the proliferation index were observed. These decreases were not a consequence of chromosome aberrations.

In Experiments I and II, no biologically or statistically significant increase of the aberration rates was reported after treatment with LegH Prep containing soy leghemoglobin compared to the solvent control cultures (Annex 5, *see* Tables 6 and 8). The χ^2 Test for trend was performed to test whether there was a concentration-related increase in chromosomal aberrations. No statistically significant increase was reported in all experimental conditions. EMS (400 and 900 µg/mL) and CPA (7.5 µg/mL) were used as positive controls and induced distinct and biologically relevant increases in cells with structural chromosomal aberrations, thus proving the efficiency of the test system to indicate potential clastogenic effects.

In conclusion, under the conditions of these studies, LegH Prep did not induce structural chromosomal aberrations in human lymphocyte cells. Therefore, LegH Prep is considered to be non-clastogenic in this chromosome aberration test.

[9] OECD Guideline for the Testing of Chemicals: *In vitro* mammalian chromosomal aberration test, TG 473. Available at: https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg473-2014-508.pdf

6.4. Assessment of Allergenicity

6.4.1 Assessment of potential soy and legume cross-reactivity

6.4.1.1 Soy Cross-Reactivity

Soybeans are acknowledged as a commonly allergenic food. Soybeans are known to contain several allergenic proteins (Taylor, Panda, Goodman, & Baumert, 2014). However, soy leghemoglobin is not identified among the known soybean allergens, nor is it detectably present in soybeans. It is the expert opinion of Dr. Taylor, co-founder and co-director of the Food Allergy Resource and Research Program (FARRP) at the University of Nebraska, that Impossible Foods does not need to perform experiments to demonstrate that LegH Prep does not cross-react with soy-allergic individuals (Annex 6). Nevertheless, Impossible Foods will notify consumers by labeling that the product "Contains Soy" as required by the statute.[10] Because Impossible Foods will identify the potential allergen on its label, there is no necessity to prove that soy-allergic individuals will not react to soy leghemoglobin.

Furthermore, the size of adult population of soy-allergic individuals is insufficient to acquire enough subjects to perform a statistically significant clinical study. While 0.4% of children are allergic to soy, the large majority of them outgrow it by the age of 10 (Savage, et al., 2010). Finally, leghemoglobin is natively expressed in the root of the soy plant, whereas the allergens – Gly m 4, Gly m 5, and Gly m 6 are located in the seeds. These allergens are completely absent from LegH Prep, which is produced by *Pichia pastoris* genetically engineered to express only soy leghemoglobin. This physical separation, as well as the lack of sequence homology to known soy allergens, indicates that soy leghemoglobin is highly unlikely to elicit a reaction in a soy-allergic consumer.

Additionally, soy leghemoglobin was evaluated to determine if this protein had the potential to become a novel food allergen. In accordance with the consensus recommendations of the Codex Alimentarius Commission, it is the opinion of Dr. Taylor that sequence homology and pepsin digest analyses are the most predictive methods known to date to assess allergenicity of novel proteins. Therefore, besides these two tests, there are no additional tests that Impossible Foods could perform that would strengthen the evidence against potential allergenicity of soy leghemoglobin.

6.4.1.2 Legume Cross-Reactivity

Clinical cross-reactivity among various foods from the legume family is rare (Bernhisel-Broadbent and Sampson, 1989). In the largest study reported to date, in 793 persistent peanut-allergic subjects, 9.5% were considered allergic to other legumes by oral challenge including 48 to soy, 19 to pea, 7 to lentil, 4 to chickpea and 3 to green bean (Neuman-Sunshine et al., 2012). Based upon the prevalence and severity of peanut allergy, potential cross-reactions between soy

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[10] While not required by the labeling statutes, in addition to the allergen statement on the business to business labeling, Impossible Foods will provide training materials and information about the product to restaurants who purchase the product, including language and instruction indicating it is a soy-protein based product.

leghemoglobin and peanut allergens is the key area of potential concern. The various peanut allergens are very well identified and characterized. No significant sequence homology exists between soy leghemoglobin and any of the peanut allergens (section 5.3.2.2). Moreover, soy leghemoglobin is found in the root of the soy plant and bears no structural resemblance or sequence homology to these seed storage proteins which are found in the peanut kernel. It is the expert opinion of Dr. Taylor that Impossible Foods does not need to perform experiments to demonstrate that LegH Prep does not cross-react with legume-allergic individuals (Annex 6).

6.4.2 Assessment of soy leghemoglobin and *Pichia* proteins within LegH Prep

The potential allergenicity of soy leghemoglobin as well as the *Pichia* proteins present in LegH Prep were assessed in the same manner as used for the novel proteins expressed in genetically engineered foods. The Codex Alimentarius Commission developed an assessment scheme for the analysis of the potential allergenicity of proteins derived from biotechnology (2003). This assessment is a multi-factorial approach which includes assessing the source of the protein for allergenicity, the sequence homology of the protein to known allergens, resistance to pepsin degradation and, if there is a high suspicion of allergenicity, specific serum screening. This analysis provides a likelihood of allergenic response by considering the totality of the evidence. Several prominent organizations support this approach: the 1996 ISLI-IFBC decision tree, the 1996 FAO/WHO consultation on biotechnology and food safety, the 2000 FAO/WHO consultation on food derived from biotechnology, the 2001 FAO/ WHO consultation on allergenicity assessment of GM foods, the 2002 Codex ad hoc task force on safety assessment of biotechnology, and the 2003 Codex Alimentarius Commission guidelines to assess the allergenicity of genetically modified crops (Metcalfe, Astwood, Townsend, Sampson, Taylor, & Fuchs, 1996) (FAO/WHO, 1996) (FAO/WHO, 2000) (FAO/WHO, 2002) (FAO/WHO., 2001) (Codex Alimentarius, 2003).

Impossible Foods enlisted Dr. Richard E. Goodman, research professor at FARRP of the University of Nebraska, to assess the potential allergenicity and toxicity of soy leghemoglobin and the *Pichia pastoris* proteins present in LegH Prep at ≥1% of the total protein fraction, consistent with the Codex recommendations. Approximately 17 *Pichia pastoris* proteins were found to be present in LegH Prep at ≥1% of the total protein fraction. These proteins are consistent from batch to batch and were identified by Impossible Foods using mass spectrometry. This multifactorial approach, which included a comprehensive literature search, sequence homology, and pepsin digestion assessments to assess the allergenic potential of new proteins, is widely used in the food industry (Fuchs, Ream, Hammond, Naylor, Leimgruber, & Berberich, 1993) (Reed, et al., 1996) (Harrison, et al., 1996) (Hileman, 2006) (Noteborn, et al., 1995) (Hashimoto, et al., 1999) (Momma, et al., 1999) (Goodman, 2007) (Moran, 2014). A summary of Dr. Goodman's evaluation is provided in Annex 7. Final reports on sequence homology and pepsin digestion are provided in Annexes 8-10.

6.4.3 Literature search

Dr. Goodman's assessment included a full literature search to identify any published literature regarding possible allergenicity or toxicity associated with leghemoglobin proteins or the *Pichia pastoris* proteins present within LegH Prep. The conclusion of this assessment was that no published literature could be found that suggested allergic, toxic or adverse health effects related to consumption of leghemoglobin or *Pichia pastoris* proteins (Annexes 8-9).

6.4.4 Sequence homology

Dr. Goodman's assessment also determined if the amino acid sequence of soy leghemoglobin or the *Pichia pastoris* proteins in LegH Prep contained sufficient similarity with any known allergen or toxin to suggest possible cross-reactivity. Soy leghemoglobin and *Pichia pastoris* protein sequences were compared to the 2016 Allergen Online Database (www.allergenonline.org) and the NCBI-Entrez database, first without any keyword selection, and again with keywords "allergen", "toxin" or "toxic". Soy leghemoglobin protein did not produce significant (>35%) homology to known allergens or toxins (Annex 8).

All of the 17 *Pichia pastoris* proteins have homologs that are ubiquitous in nature. Therefore, a search of the NCBI database for sequences related to each of the 17 proteins, using BLASTP without keyword limits, identified good alignments with related proteins from many molds and yeasts. For all 17 proteins, these alignments included *Saccharomyces cerevisiae* and *Saccharomyces bayanus*, which are commonly used in making wine, bread, and beer, and *Saccharomyces boulardii*, which is widely used as a probiotic (Moyad, 2008) (Munoz-Bernal, 2016) (Liu, 2016). The long history of consumption of these close homologs of all 17 *Pichia pastoris* proteins with no reports of allergenicity or toxicity offers strong general evidence for their safety in food (Annex 9).

Bioinformatics searches with the 17 most abundant residual *Pichia pastoris* proteins found in LegH Prep identified a few related protein sequences with sufficient similarity to exceed the Codex suggestion for potential cross reactivity (>35%) (Table 6). However, the sequence-related putative allergens identified in this search were not potent, common allergens, nor were any of them known to be allergenic when ingested. Moreover, comparison of the same *Pichia pastoris* proteins with all proteins in the NCBI Protein database identified far more significant matches to proteins found in commonly consumed fungi, including baker's yeast (*Saccharomyces* species).

Table 6. Summary of sequence alignments for Soy Leghemoglobin and the 17 most abundant residual *Pichia pastoris* proteins found in LegH Prep.

Protein Name	GeneInfo Identifier	Accession	No. of AA[1]	AOL[2] Matched Allergen[3]	AOL Best ID[4]	*Saccharomyces sp.* Best ID
Soy leghemoglobin	126241	P02236.2	145	n/a[5]	n/a	n/a
Alpha aminoadipate reductase	238030060	CAY67983.1	1400	n/a	n/a	60%
Cobalamin-independent methionine synthase	238030843	CAY68766.1	768	Sal k 3	77.50%	77%
Aconitase	254564667	XP_002489444.1	780	n/a	n/a	81%

Transketolase	238030057	CAY67980.1	679	n/a	n/a	70%
Glycerol kinase	238034027	CAY72049.1	621	n/a	n/a	53%
Catalase A	254569930	XP_002492075.1	510	Pen c 30	60%	66%
G6PD	-238031000	CAY68923.1	504	Bla g 3	37%	64%
Hypothetical protein PAS	238031215	CAY69138.1	525	Cla h 10	72.50%	69%
				Alt a 10	72.50%	
				Lep d 13	35.40%	
Mitochondrial aldehyde dehydrogenase	238033249	CAY71271.1	501	Cla h 10	76.20%	62%
				Alt a 10	76.20%	
Delta-aminolevulinate dehydratase	238033645	CAY71667.1	341	n/a	n/a	76%
Mitochondrial alcohol dehydrogenase isozyme III	238031179	CAY69102.1	350	Cand a 1	85%	74%
Malate dehydrogenase	238034064	CAY72086.1	342	Mala f 4	70%	57%
				Pis s 2	36.20%	
Putative protein, unknown function	238033788	CAY71810.1	328	n/a	n/a	86%
Triose phosphate isomerase	238032989	CAY71012.1	248	Tri a 31	62.50%	71%
				Der f 25.0101 (isoform)	60.00%	
				Der f 25.0201 (isoform)	60.00%	
				Cra c 8	57.50%	
Hypothetical protein (cyclophilin) PP7435	328350030	CCA36430.1	161	Mala s 6	87.50%	74%
				Asp f 27	85%	
				Cat r 1	81.30%	
				Der f 29	80%	
				Asp f 11	80%	
				Bet v 7	80%	
				(Unassigned by IUIS) PPIase[6] from *Dauces carota*	78%	
Cytosolic superoxide dismutase	238034030	CAY72052.1	154	Ole e 5	60% - 55%	79%
				23 isoforms		

Mitochondria ATPase Inhibitor	238029769	CAY67692.1	84	n/a	n/a	62%

[1]AA: amino acids;
[2]AOL: AllergenOnline
[3]Allergen name in IUIS allergen list unless denoted as unassigned by IUIS;
[4]ID: identity (%);
[5]n/a: not available or no answer.
[6]PPIase: peptidylprolyl isomerase.

While a number of organisms with known toxicity (e.g., *Bacillus sp., Enterococcus faecalis, Streptomyces sp., Clostridium sp.*) contained proteins with sequences similar to those of the *Pichia pastoris* proteins of interest, these proteins were ubiquitous and highly conserved across diverse species, and are not themselves known or suspected to be toxic. As a further evaluation step, a comparison of the sequence-related proteins from toxin-producing species with proteins from diverse non-toxic species revealed far more closely-related proteins from sources that are known to be safe and non-toxic (Annex 9).

AllergenOnline (AOL) has been updated every year since 2004. A panel of allergen experts evaluates each entry using published acceptance criteria (Goodman et al. 2016). AOL is based on published studies characterizing the proteins and evidence for their allergenicity using allergic human subjects as challenge subjects, serum donors, or basophil donors in well-accepted methods. In addition to using the AOL database, the NCBI protein database, which is updated weekly, was queried to identify any sequences that may have been identified after the most recent AOL update.

While the information discussed above is more than adequate to demonstrate that both soy leghemoglobin and the *Pichia* proteins within LegH Prep have little or no allergenic potential, Impossible Foods was encouraged to conduct a support-vector machine (SVM) analysis.[11] While Impossible Foods is aware that there is some controversy as to the reliability of this method, Impossible Foods agreed to perform an SVM analysis for soy leghemoglobin.

In addition to the AOL method, Impossible Foods identified eleven alternative support vector machine-based (SVM-based) methods to assess potential allergenicity, five of which had active, useable web interfaces (Tables 7 and 8).

Four of the five SVM-based methods indicated that soy leghemoglobin is not an allergen (Table 7), in concurrence with the AOL method. Although, a fifth SVM-based test, AlgPred, indicated that soy leghemoglobin may be a potential allergen, further investigations into the methodology underlying AlgPred suggest that it may have a high false positive rate. For example, AlgPred identifies 46% of all proteins in SwissProt as potential allergens, even after all known allergens and related proteins have been removed from the SwissProt database (Saha and Raghava, 2006). However, a conservative assumption is that only small percentage of proteins are potential allergens. Based on the weight of evidence (concurrence between AOL and 4

[11] This analysis was not conducted or endorsed by FARRP or Dr. Goodman.

alternative SVM-based methods) and the potential methodological pitfalls of AlgPred, soy leghemoglobin has a low potential risk of allergenicity.

Table 7. Summary of SVM-based methods and results.

Name	**Website**	**Brief Description**	**Result**	**Comments**
PREALw	http://lilab.life.sjtu.edu.cn:8080/prealw/predict.html	Weighted average assessment based on SVM and sequence searches suggested by FAO*	Non allergen	
AlgPred	http://webs.iiitd.edu.in/raghava/algpred/submission.html	AlgPred uses five different methods to assess allergenicity.	Mixed**	Published version of website is non-functional but author was contacted to obtain functioning link
SVMProt	http://bidd2.nus.edu.sg/cgi-bin/svmprot/svmprot.cgi	Is a broad SVM classifier of protein function. One of the categories they train their predictor against is whether or not the protein is a known allergen.	The SVMProt classifier does not predict that soy leghemoglobin is an allergen.	
SortAller	http://sortaller.gzhmu.edu.cn/	SORTALLER is an online SVM based allergen classifier based on the allergen family featured peptide (AFFP) dataset.	SORTALLER predicted the query sequence soy leghemoglobin as a non-allergen with score of 0.265	

* A protein is identified as a putative allergen if it contains at least six contiguous exact amino acids matches (rule 1) or at least 35% sequence similarity within an 80 amino acid window (rule 2) when compared with known allergens (Wang, 2013)

** The AlgPred algorithm uses five different classifiers. Three (mapping of IgE motifs, a search for allergen related motifs and a BLAST search of the database) are negative for potential allergenicity. The two (closely related) SVM classifiers suggest that soy leghemoglobin is a potential allergen based on its amino acid composition.

Table 8. Non-functional SVM-based sites.

Name	Website	Status (as of August 21, 2017)
ProInFlam	http://metagenomics.iiserb.ac.in/proinflam/prot.php	Website exists but searches using all available tools on the site return errors and no results.
Allerdictor	http://allerdictor.vbi.vt.edu/	Website online but search returns error.
AllergenFP	http://ddg-pharmfac.net/AllergenFP/	Website online but search returns error.
AllerHunter	http://tiger.dbs.nus.edu.sg/AllerHunter	Website offline.
WebAllergen	http://nabic.rda.go.kr/allergen/allergenIntroduction.do	Search not available.
FuzzyAPP	http://fuzzyapp.bicpu.edu.in/	Webserver not available.

6.4.5 Pepsin digestion

Dr. Goodman assessed the stability of the soy leghemoglobin and the *Pichia pastoris* proteins within LegH Prep to pepsin degradation in a simulated gastric fluid. Several peer-reviewed studies have shown that low *in vitro* pepsin digestibility is an important risk factor for food allergy (Astwood, 1996) (del Val, 1999). Bannon *et al.* (2003) reviewed a broad range of published pepsin digestion studies and found a strong positive predictive value of the digestion protocol when comparing the stability of allergenic and non-allergenic dietary proteins (Bannon, 2003). A published multi-laboratory study demonstrated the rigor and reproducibility of using pepsin digestion to evaluate the stability of a number of food allergens and non-allergenic proteins across nine laboratories (Thomas, 2004). The pepsin digest protocol conducted in the Goodman Lab is identical to the robust procedure used in Thomas *et al.*, 2004. In addition to the recommended ratio of 10 U pepsin enzyme to 1 μg target protein, the Goodman lab also evaluated a more stringent ratio of 1 U enzyme to 1 μg target protein. Dr. Goodman's laboratory-based assessment demonstrated that soy leghemoglobin protein as well as the *Pichia pastoris* proteins are readily digested by pepsin at ratios of 10 U pepsin enzyme to 1 μg target protein and 1 U enzyme to 1 μg target protein, confirmed with SDS-PAGE analysis (Annex 10). It is the expert opinion of Dr. Goodman that using a lower than standard activity of pepsin in this assay is not scientifically justified due to insufficient published data on the sensitivity of known allergens and non-allergenic proteins under these conditions, and thus the inability to interpret the results.

In summary, based on a weight of evidence approach including literature search, sequence homology analysis and pepsin digestion, Dr. Goodman concluded that consumption of the soy leghemoglobin protein as well as the *Pichia pastoris* proteins present in Impossible Foods' LegH Prep raise no health or safety concern as they do not pose any significant risk of allergy (Annex 7).

6.4.6 Assessment of potential cross-reactivity with meat allergic individuals

Tick-bite induced allergy to mammalian meat (e.g., beef, pork) and organs (e.g., liver, kidney) has been reported in the United States, Europe, Australia and parts of Asia (Stinke JW, 2015). However, the allergic reaction is due to an IgE antibody response to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal), which is located on glycoproteins and glycolipids in non-primate mammalian meat and organs (Commins SP, 2016). The allergic reaction is not caused by myoglobin, and therefore consumers with alpha-gal specific IgE antibodies will not cross-react with soy leghemoglobin.

Impossible Foods is aware of only a single case of meat allergy linked to bovine myoglobin (Fuentes et al., 2004), although implication of bovine myoglobin in this case has been disputed (Fiocchi et al., 2005). The reactions reported in this patient were specific to bovine myoglobin, and not porcine myoglobin, suggesting that this is not a general allergy to oxygen-binding globin proteins, but rather a specific response to a bovine-derived protein. Given the widespread consumption of meats containing oxygen-binding globins at concentrations comparable to those proposed for use of soy leghemoglobin in this notification, the low incidence of meat allergies in general (and the cause of those few reactions is predominantly due to bovine serum albumin sensitivities), and only a single reported case of myoglobin allergy, this argues that these proteins as a class have low allergenicity.

6.5 Summary of Safety Testing

LegH Prep is a solution of proteins, containing not less than 65% soy leghemoglobin, plus proteins from the yeast *Pichia pastoris*. These components were evaluated for history of safe use as well as potential risks of allergenicity, general toxicity in rats, and genotoxicity.

The Impossible Foods' *Pichia pastoris* production strain is derived from a strain lineage with a long history of safe use. *Pichia* is non-pathogenic and non-toxigenic (21 CFR Part 573). *Pichia* has been used to express proteins for use in human food (GRN 204), potable water treatment (The Nitrate Elimination Co. Lake Linden, MI), animal feed (AAFCO, 2013), and FDA approved therapeutics. Although the soy leghemoglobin protein does not have a history of wide consumption in the human diet, heme B-containing proteins, which contain the chemically identical heme B co-factor (Annex 1), have been safely consumed in meat and plants throughout human history. Moreover, the soy leghemoglobin polypeptide does not pose any significant risk of allergy or toxicity.

LegH Prep was evaluated for potential risk of allergenicity using a weight of evidence approach in accordance with the 2003 Codex Alimentarius Commission guidelines for assessment of potential allergenicity of proteins derived from biotechnology. No published literature could be found that suggested allergic, toxic, or adverse health effects related to consumption of soy leghemoglobin or *Pichia pastoris*. The soy leghemoglobin protein does not contain significant (greater than 35%) sequence homology to known allergens or toxins. The most abundant *Pichia* proteins within LegH Prep are ubiquitous in nature and contain high sequence identity to homologues in yeast and molds that are commonly used in making cheese, wine, bread, and beer. LegH Prep is rapidly digested by pepsin in a simulated gastric fluid. Although there is no scientific evidence to suggest that soy-allergic individuals will cross-react with soy leghemoglobin, Impossible Foods will include "soy" on the label. In addition, Impossible Foods will notify consumers that the product "Contains Soy."

LegH Prep showed no evidence of toxicity in rats at the maximum dose tested, which was 750 mg/kg/day soy leghemoglobin. In a 28-day GLP feeding study in rats (43166), there were no clinically significant differences between groups in clinical observations, body weights, hematological parameters, clotting potential, or clinical chemistry for both sexes. In the male rats, there were no test article-related macroscopic or microscopic findings or differences in absolute organ weights and organ weight to body ratios. In the female rats, it was suggested that there might be a test article-related effect on the estrous cycle. However, a follow up 28-day feeding study (44856) with estrous cycle monitoring confirmed that there were no test article-related effects on the female rat estrous cycle or reproductive organs at the maximum dose of 750 mg/kg/day soy leghemoglobin, the highest dose tested. The NOAEL is used to determine. the Acceptable Daily Intake (ADI). The NOAEL is divided by an acceptable Uncertainty Factor, 100 fold is generally accepted.[12] The ADI for soy leghemoglobin is 750/100 or 7.5 mg/kg/day. The 90th percentile EDI for soy leghemoglobin is 6.67 mg/kg/day. Since the EDI is lower than the ADI, there are no suggested safety concerns.[13]

Genotoxicity of LegH Prep was assessed using the bacterial reverse mutation assay and the chromosomal aberration assay in human lymphocytes. LegH Prep was found to be non-mutagenic and non-clastogenic in each assay.

In conclusion, LegH Prep does not appear to present any significant issues of safety that would preclude its use in meat analogue products.

6.6 Expert Panel Report

The Expert Panel Report is included in the following pages.

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[12] The food additive regulations recommend a safety factor of 100, in the absence of extenuating circumstances. 21 C.F.R. 170.22.

[13] FDA. Chapter II: Agency Review of Toxicology Information in Petitions for Direct Food Additives and Color Additives Used in Food. Available at: https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/UCM078724.pdf

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The Report of the Expert Panel on the Generally Recognized as Safe Determination of the Proposed Uses of Soy Leghemoglobin Protein Derived from *Pichia pastoris* as a Food Ingredient

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Introduction

Impossible Foods Inc. (Impossible Foods) convened a panel of independent scientists (Expert Panel), qualified by their scientific training and relevant national and international experience in the evaluation of the safety of food ingredients, to conduct an independent, critical and comprehensive evaluation of the available safety information on soy leghemoglobin protein preparation (LegH Prep), and to determine if the proposed uses as a protein component in ground beef replacement (analogue) products would be Generally Recognized as Safe (GRAS) based on scientific procedures. The Expert Panel consisted of Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine), Professor Michael W. Pariza, Ph.D. (University of Wisconsin-Madison), and Professor Stephen L. Taylor Ph.D. (University of Nebraska-Lincoln).

An initial review was conducted and a summary of the results was made available to the Expert Panel as part of the "GRAS NOTIFICATION FOR SOYBEAN LEGHEMOGLOBIN PROTEIN DERIVED FROM *PICHIA PASTORIS*" (not dated) and a "TECHNICAL SUMMARY OF SOYBEAN LEGHEMOGLOBIN PROTEIN DERIVED FROM *PICHIA PASTORIS* " (dated May 30, 2014). Impossible Foods conducted further studies to confirm the safety and GRAS status of the proposed uses of LegH Prep and made this information and data available to the Expert Panel. A comprehensive search of the scientific literature on plant and animal hemoglobins and related products was conducted by Impossible Foods as part of the preparation of the new GRAS notice that is the subject of this report, as well as during the preparation of the supportive Technical Summary. Impossible Foods reported to the Expert Panel that their search failed to identify anything further on the safety of LegH Prep. The Expert Panel, independently and collectively, critically evaluated the new information and data and re-evaluated the original information and data, and other information deemed appropriate or necessary and information pertaining to the method of manufacture, product specifications, batch analyses, intended levels of use, exposure estimates, and the safety of LegH Prep.

Following its independent, critical evaluation of the available information, the Expert Panel convened by teleconference and email correspondence, and unanimously concluded that the intended use in ground beef analogue products of soy leghemoglobin protein derived from *Pichia pastoris*, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food-grade specifications, is GRAS based on scientific procedures. A summary of the basis for this conclusion appears below.

Impossible Foods proposes to market the soy leghemoglobin protein produced in the yeast *Pichia pastoris* in the United States for use as a protein component to create a flavor impact in ground beef analogue products.

Hemoglobin proteins are found in most organisms, including bacteria, protozoa, fungi, plants and animals (Hardison, 1998). Hemeproteins are classified as globin/non-globin and symbiotic/non-symbiotic. Hemoglobin, myoglobin, and leghemoglobin are examples of globin proteins. Cytochrome oxidases, hemocyanins, and methemalbumin are examples of non-globin hemeproteins (Everse, 2004) (Jokipii-Lukkari, Frey, Kallio, & Haggman, 2009). Plant hemoglobins are classified according to function as symbiotic or non-symbiotic (Gupta, Hebelstrup, Mur, & Igamberdiev, 2011). Symbiotic hemoglobins are found predominantly in leguminous plant species. The most studied symbiotic hemoglobins are the leghemoglobins of nitrogen fixing legumes where they facilitate oxygen diffusion within root tissues. Non-symbiotic hemoglobins have been identified in a wide range of legume and non-legume plants. The highest expression levels for non-symbiotic plant hemoglobin are observed in metabolically active or stressed tissue (Anderson, Jensen, Leewellyn, Dennis, & and Peacock, 1996).

Impossible Foods analyzed structures of plant non-symbiotic hemoglobins and symbiotic leghemoglobins and animal myoglobins including rice, soy, corn, barley, lupine, horse, tuna, and pig. Animal myoglobins, plant leghemoglobins and plant hemoglobins adopt the same globin fold and are structurally very similar. All globin proteins described above bind the chemically identical heme B prosthetic group involved in binding and/or transport of oxygen. The globin protein family is large, present in a wide range of organisms, and is well studied.

Identity and Characterization of Soy Leghemoglobin Protein

The chemical name of the characterizing component of LegH Prep is soy leghemoglobin protein. The source of the protein is the soybean plant *Glycine max* gene *LGB2*. Soy leghemoglobin protein is derived from the root nodules of the soy plant.

There is no Chemical Abstracts Number for soy leghemoglobin.

The proposed common or usual name of LegH Prep is "leghemoglobin (soy)."

Production of LegH Prep

The method of production involves four stages: construction of the production strain of *Pichia pastoris*, expression of soy leghemoglobin protein in submerged fermentation, enrichment, and stabilization of the expressed soy leghemoglobin protein.

All materials used in the production of LegH Prep are food grade and GRAS or high-quality chemical or pharmaceutical grades (USP, NF, or ACS grades) from approved suppliers and processing conditions are appropriate for food production and consistent with cGMP.

Preparation of the Production Strain for Fermentation

Production strain *Pichia pastoris* MXY0291 was constructed from recipient strain Bg11 (MXY0051) using a series of transformations with different expression constructs, in order to express soy leghemoglobin protein. In addition to the protein coding sequence for soy leghemoglobin, MXY0291 contains extra copies of native *Pichia pastoris* heme biosynthetic enzymes and modified *Pichia pastoris* transcription factor Mxr1, all expressed under the strong native *Pichia pastoris* alcohol oxidase promoter (*pAOX1*). This promoter has been demonstrated to produce high levels of recombinant proteins after producing biomass on glycerol and inducing *pAOX1* with methanol (Cereghino & Cregg, 2000). The genome of MXY0291 is fully sequenced and well characterized.

The production strain parent, *Pichia pastoris* Bg11, was derived from the well-characterized strain Y-11430, which is deposited in the collection at the Northern Regional Research Laboratories (NRRL). The lineage of *P. pastoris* strain NRRL Y-11430 was previously included in GRN 204, reviewed by the Agency in 2006.

There are no indications that *P. pastoris* has been associated with animal or human illness. The first *P. pastoris* strains were isolated from an oak tree and a chestnut tree and were deposited in the collection at the Northern Regional Research Laboratories (NRRL) (www.biogrammatics.com). Yeast strains screened by Phillips Petroleum for growth on methanol included two *P. pastoris* strains, designated NRRL Y-1603 (ATCC accession 28485) (ATCC, 2006b) and NRRL YB-4290 (NCAUR, 2006). Phillips Petroleum identified a *P. pastoris* strain with improved growth characteristics. The strain was designated 21-1 and deposited at NRRL, as NRRL Y-11430 . This strain is now available from ATCC as 76273. No records are available confirming that NRRL Y-1603 or NRRL YB-4290 is the progenitor of NRRL Y-11430, but it seems likely that one of them is the progenitor strain. NRRL Y-11430 was the progenitor strain for GS115, a histidine auxotrophic mutant *(his4-)*, a common *Pichia* strain provided in commercial kits by Invitrogen Corporation, and widely used as the parental strain of many biotechnology products, including FDA approved proteins such as Kalibitor® (ecallantide, for the treatment of acute attacks of hereditary angioedema, 2009). Additionally, the GS115 derived strain SMD1168 is used for the GRAS approved production of BD16449 Phospholipase C (Food and Drug Administration, 2006). Like GS115, the BioGrammatics, Inc. strain, Bg11 is also a derivative of NRRL Y-11430, and genomic sequencing data performed by BioGrammatics Inc. confirm the similarity of NRRL Y-11430, Bg11 and GS115. Additional taxonomic history of these strains is available in a 2009 manuscript by C. Kurtzman and on the Biogrammatics webpage (biogrammatics.com).

BioGrammatics, Inc. further developed the NRRL-Y-11430 strain to remove the native *P. pastoris* plasmids using PCR primers unique to the plasmids to screen multiple single-colony isolates for the presence of the plasmids. One isolate without plasmids was selected to become the wild-type (wt) BioGrammatics strain, Bg10. Genomic sequence from Bg10 indicates the plasmids are no longer present, and, benchmarks the similarity of Bg10 with NRRL-Y11430, as well as with GS115. Biogrammatics, Inc. deleted the gene encoding for Aox1 from Bg10 using homologous recombination to generate Bg11, a strain that grows more slowly on methanol-containing induction media. Like NRRL Y-11430 and GS115, Bg11 does not contain antibiotic resistance genes.

Expression of Soy Leghemoglobin Protein in Submerged Fermentation, Enrichment and Stabilization

Soy leghemoglobin protein is obtained by fed-batch fermentation using the *P. pastoris* production strain MXY0291 described above. All media components are FCC approved or food-grade ingredients. The *P. pastoris* cells in the fermentation broth are lysed by bead mill mechanical shearing. Insoluble material within the lysate is removed by centrifugation and microfiltration. Ultrafiltration is used to concentrate soy leghemoglobin protein to at least 60 g/l. The resulting concentrated sample is stabilized with sodium chloride and sodium ascorbate and stored as a frozen liquid.

Specifications for Soybean Leghemoglobin Protein Product

LegH Prep is standardized to contain at least 60 grams per liter (g/l) soy leghemoglobin protein. Sodium chloride and sodium ascorbate are used to stabilize the product. All stabilizing agents are food grade. The product specifications, and batch analysis results, are presented below.

Table 1. LegH Prep specifications and batch analyses from five independent production runs.

	Specifications	PP-PGM2-16-015-101	PP-PGM2-16-088-101	PP-PGM2-16-102-101	PP-PGM2-16-144-101	PP-PGM2-16-200-101
Soy Leghemoglobin Protein (w/w)[1]	6 – 9%	6.74%	6.39%	6.28%	6.74%	6.95%
Soy Leghemolglobin Protein Purity (w/w)	≥65%	82%	71%	85%	77%	86%
Fat (w/w)	≤2%	0.05%	<0.01%	<0.01%	0.03%	0.08%
Carbohydrates (w/w)	≤4%	1.72%	0.99%	1.67%	2.01%	2.73%
Ash (w/w)	≤4%	1.87%	0.67%	2.63%	2.62%	2.74%
pH	6.5 – 8.5	7.19	7.19	7.38	7.01	6.77
Lead (ppm)	<0.4	<0.01	<0.01	<0.01	<0.01	<0.01
Arsenic (ppm)	<0.05	0.01	<0.01	<0.01	0.01	<0.01
Mercury (ppm)	<0.05	<0.005	<0.005	<0.005	<0.005	<0.005
Cadmium (ppm)	<0.2	<0.001	<0.001	0.001	0.003	0.001
Aerobic plate count (CFU/g)[2]	<10^4	<10	<10	<10	<10	<10
E. coli 0157:H7[3]	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test
Salmonella spp.[4]	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test
Listeria monocytogenes[5]	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test	Absent by test

Stability of Soy Leghemoglobin

LegH Prep has been stored at -20 °C as a frozen liquid for at least 12 months with no observable change in soy leghemoglobin protein stability or performance in ground beef analogue products.

Intended Uses in Food

LegH Prep is proposed to be used as a plant-based protein component in non-animal derived food products with the texture, nutrition, flavor and appearance of traditional animal derived foods. LegH Prep will impart a unique flavor impact to meat analogue products.

The high bioavailability of the heme iron component of soy leghemoglobin makes it suitable to enhance the dietary profile of many processed foods (Carpenter & Mahoney, 1992).

LegH Prep may be one of several Food and Drug Administration ("FDA" or "Agency") recognized plant proteins that will comprise ground beef analogue products. Other proteins may include, but are not limited to, commercially available proteins from soy, pea, mung bean, lentil, corn, potato, and wheat. Soy leghemoglobin will function to contribute to the flavour and nutritional quality of ground beef analogue products. A typical ground beef analogue product may contain:

Component	Meat Analogue
Protein	10%-25%
Plant Oils	0%-25%
Miscellaneous+	2%
Water	50%-75%

+Miscellaneous ingredients may include salt, flavors, vitamins, essential amino acids, etc.

LegH Prep will be added to the ground beef analogue products to deliver not more than 0.8% soy leghemoglobin protein.

Self-limitation of the Use of Soybean Leghemoglobin Protein Product

The use of LegH Prep in ground beef analogue products above the specified use-levels is largely self-limiting based on unacceptable organoleptic properties.

Estimated Dietary Intake

The vast majority of hemeproteins consumed in the diet are as myoglobin through consumption of meat and poultry products. Hemeprotein consumption was estimated using data from the "Retail Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08. (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). For the US population, per capita mean consumption of meat and poultry products is 154 g/day and the 90th percentile intake is 308 g/day. Assuming an average myoglobin concentration for meat and poultry products of 0.5% (Yip & Dallman, 1996), the average per capita myoglobin consumption would be 0.77 g/day and the 90th percentile intake would be 1.54 g/day.

LegH Prep will be marketed for use in ground beef analogue products that provide consumers a flavorful and nutritious alternative to meat containing products. Impossible Foods has estimated daily intakes of soy leghemoglobin protein by assuming consumers will substitute the meat analogue product for the traditional meat product on a 1-for-1 basis.

Impossible Foods has assumed it will capture 100% of the total ground beef market with soy leghemoglobin protein-containing ground beef analogue products. 100% of the total ground beef market represents approximately 500 times the volume of the current meat analogue market size based on sales estimates[1]. The Estimated Daily Intake (EDI) of soy leghemoglobin in the target ground beef analogue applications was established using the Retail Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08 (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). The results of that analysis are presented below. The estimates were calculated as follows:

For beef, the mean daily consumption is 59 grams. For ground beef, the mean consumption is 25 grams (59 grams x 42%). As the highest usage case, Impossible Foods assumes capturing 100% of this market with a ground beef analogue product consisting of not more than 0.8% soy leghemoglobin. This equates to a highest intake case of 200 mg/person/day of soy leghemoglobin (25 ground beef grams/person/day x 100% market x 0.8% soy leghemoglobin).

The estimated average daily intake of soy leghemoglobin in the intended applications will be 150 mg/person/day (0.6% soy leghemoglobin) and the maximum intake will be 200 mg/person/day (0.8% soy leghemoglobin). As noted above, this base case represents capturing 500 times the existing meat and poultry analogue market.

[1] Datamonitor estimates the US meat analogue volume was 53M kg in 2009. USDA-FAS Livestock and Poultry Report, April 2014 estimates 2014 US consumption of 11B kg beef, 8.5B kg pork, and 14B kg broilers. Therefore, the current meat analogue market is less than 0.2% of the overall meat market and capturing 1% of the meat market represents 5 times the current meat analogue market in the US.

Table 2a. Summary of proposed uses of soy leghemoglobin protein in food applications based on Retail Food Commodity Intakes 2007-2008.

Food Category to be Replaced	Mean Consumption (g/day)[2]	Anticipated Market Share Replacement (%)	Anticipated Typical Use rate (%)	Soy Leghemoglobin Estimated Typical Daily Intake (mg/person/day)	Anticipated Maximum Use Rate (%)	Soy Leghemoglobin Estimated Maximum Daily Intake (mg/person/day)
Ground Beef	25	100	0.6	150	0.8	200

Table 2b. Summary of proposed uses of LegH Prep dry solids in food applications based on Retail Food Commodity Intakes 2007-2008.

Food Category to be Replaced	Mean Consumption (g/day)	Anticipated Market Share Replacement (%)	Anticipated Typical Use rate (%)	LegH Prep Dry Solids Estimated Typical Daily Intake (mg/person/day)	Anticipated Maximum Use Rate (%)	LegH Prep Dry Solids Estimated Maximum Daily Intake (mg/person/day)
Ground Beef	25	100	0.6	404	0.8	539

For the basis of safety testing, the 90th percentile consumption of soy leghemoglobin was calculated using 25 grams ground beef/person/day x 0.8% soy leghemoglobin/ground beef / 60 kg/person x 2. Therefore, the 90th percentile consumption equates to 6.67 mg/kg/day, which was used as the basis for safety testing.

Safety of Soy Leghemoglobin

Hemeproteins are found in bacteria, protozoa, fungi, plants and animals (Everse, 2004) (Hardison, 1998). Soy plants have been shown to express three hemoglobin proteins: symbiotic, non-symbiotic and truncated (Lee, Kim, & An, 2004). Symbiotic plant hemoglobins, which evolved from non-symbiotic hemoglobins (Gupta, Hebelstrup, Mur, & Igamberdiev, 2011), are commonly referred to as leghemoglobins. Symbiotic leghemoglobins, found predominately in legume root nodules, function in the nitrogen fixation process in concert with the bacterium *Rhizobium* where they facilitate oxygen diffusion within host root tissues. LegH Prep contains this symbiotic soy leghemoglobin derived from *Pichia pastoris*.

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[2] Retail Food Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08. U.S. Department of Agriculture, Agricultural Research Service, Beltsville, MD and US Department of Agriculture, Economic Research Service, Washington, D.C.
http://www.ncaur.usda.gov/SP2UserFiles/Place/12355000/pdf/ficrcd/FICRCD_Intake_Tables_2007_08.pdf

Anderson et al. demonstrated that the non-symbiotic hemoglobin in soybeans was expressed in various plant tissues including stems, shoots, cotyledon, leaves, and root hair (Anderson, Jensen, Leewellyn, Dennis, & and Peacock, 1996). These soybean tissues are commonly consumed in the diet in the form of bean sprouts. Commercial production of soybean sprouts is a six (6) day process from imbibition to packaging for retail sale (Lim, 2014). Sprouted barley, which is widely used in the beverage industry (malted barley) and in the baking industry (malted barley flour), has been reported to express hemoglobin one (1) day after imbibition (Duff, Guy, Xianzhou, Durnin, & Hill, 1998). Non-symbiotic hemoglobins are expressed in the rice embryo and in the coleoptiles and seminal root of sprouted rice, which are consumed as part of the diet (Lira-Ruan, Ruiz-Kubli, & Arredondo-Peter, 2011).

Impossible Foods analyzed plant symbiotic leghemoglobins (soy, lupine), non-symbiotic plant hemoglobins (rice, corn, barley), and animal myoglobins (horse, tuna, pig) and confirmed the structural similarity (cf. Annex 1, GRASN). The three dimensional structure of soybean leghemoglobin is highly similar to the non-symbiotic hemoglobins of corn, rice, and barley as well as mammalian myoglobin.

Globin proteins bind the identical heme prosthetic group and are involved in binding or transporting oxygen. The oxygen binding mechanism of soy leghemoglobin is similar to that of animal muscle myoglobin.

History of Safe Use

The safety of soy protein is well established. Soybeans have been part of the human diet for more than 5000 years.

In the 2004/2005 marketing year, 229 million metric tons of soybeans were produced worldwide. Although the majority of the crop is used for animal feed, approximately 14% is used for human food in the form of traditional soyfoods, e.g. tofu, soymilk, natto, miso, bean sprouts, and as soy protein ingredients used to formulate food products as diverse as infant formula, dairy and meat alternatives, nutritional supplements and energy bars. (Golbitz & Jordan, 2006) Plant and animal hemoglobin proteins are widely consumed in the human diet where they represent a highly bioavailable source of dietary iron for human nutrition. Plant-derived hemoglobins are prevalent in our food system through malted grain products and sprouted beans (pulses).

Regulatory Status

The use of soy proteins is widely accepted in the United States. The US Food and Drug Administration has affirmed the safety of soy protein isolates for inclusion in many products and has approved a health claim for soy protein and the reduced risk of coronary heart disease (21 CFR 101.82). In 2000, the US Department of Agriculture issued a ruling allowing soy protein to completely replace animal protein in the National School Lunch Program (Messina, 2006). The safety of soy protein in human food has been clearly established and affirmed by the two major food regulatory agencies in the US.

Repeated Dose (28-Day) Toxicity Studies in CRL- Sprague-Dawley-CD® IGS Rats

Two studies were conducted by Product Safety Laboratories (Dayton, NJ) consistent with OECD GLP Guidelines and with OECD Guidelines 407 and FDA'S Red Book for the initial study (43166) and with OECD Guideline 421 for the follow-up study (44856). Experimental and environmental conditions were the same including doses of LegH Prep (0, 250, 500, 750 mg soy leghemoglobin protein/kg bw/day), mode of administration (dietary admixture) and species and strain of rats.

In the initial study, although there were no consistent, dose-dependent, statistically significant treatment-related adverse effects reported, a NOAEL was not determined since potential perturbations on estrous cyclicity were reported at the low and high dose but not the middle dose. This lack of a dose-response suggested these effects were not treatment-related. Upon the advice of its scientific consults and as part of its products stewardship program, Impossible Foods secured the services of Dr. Karen Regan, an internationally recognized expert in reproductive toxicology, to review the results of this study and to assist in the design and execution of a follow up study, if deemed advisable. It was determined that OECD Guidelines for evaluating estrous activity (OECD 421) were most appropriate. The study was successfully executed. Dr. Regan independently completed her critical evaluation of the data and then reviewed her findings with the study pathologist who examined the tissues from the initial study. Dr. Regan and Product Safety Labs concluded that there were no test-substance related effects on reproductive macroscopic and microscopic parameters/observations, reproductive organ weights or estrous cyclicity in either study. The NOAEL was determined to be the highest dose tested, 750 mg soy leghemoglobin protein/kg bw/day. The Expert Panel concurs with these conclusions, there are no LegH Prep-related adverse effects on rat estrous cyclicity and the NOAEL is 750 mg soy leghemoglobin protein/kg bw/day.

Allergenicity

Soybeans are acknowledged as a commonly allergenic food. Soybeans contain several allergenic proteins (Taylor, Panda, Goodman, & Baumert, 2014). Soy leghemoglobin is not identified among the known soybean allergens. Moreover, soy leghemoglobin is expressed in the root nodules of the soy plant rather than the bean. The potential allergenicity of soy leghemoglobin and the most abundant *Pichia pastoris* proteins (17 in total) present within LegH Prep can be assessed in the same manner as used for the novel proteins expressed in genetically engineered foods. The Codex Alimentarius Commission developed an assessment scheme for the analysis of potential allergenicity of proteins derived from biotechnology (Codex Alimentarius, 2003). This assessment is a multi-factorial approach which includes assessing the source of the protein for allergenicity, the sequence homology of the protein to known allergens, resistance to pepsin degradation and, if there is a high suspicion of allergenicity, specific serum screening. This analysis provides a likelihood of allergenic response by considering the totality of the evidence.

In its search of the biomedical literature, Impossible Foods did not find any publications implicating soy leghemoglobin or the 17 Pichia proteins in allergenicity or toxicity. Impossible Foods then enlisted Dr. Richard E. Goodman at the Food Allergy Resource and Research Program (FARRP) of the University of Nebraska to assess the potential allergenicity and toxicity of LegH Prep. Dr. Goodman conducted a comprehensive search of the biomedical literature to identify any published reports regarding possible allergenicity or toxicity associated with leghemoglobin and the Pichia proteins and any reports regarding health issues associated with human consumption. No negative reports were found.

Bioinformatics searches (amino acid sequence comparisons) were performed comparing the known sequence of soy leghemoglobin (GI:126241) and the 17 Pichai protein with known or putative allergens listed in the AllergenOnline.org, version 16 database using both FASTA full-length sequence alignments and search for 80 amino acid matches along the entire sequence looking for >35% identity. No significant alignments were found with soy leghemoglobin. Bioinformatics searches with the 17 most abundant residual *Pichia pastoris* proteins found in LegH Prep identified a few related protein sequences with sufficient similarity to exceed the Codex suggestion for potential cross reactivity (>35%). However, the sequence-related putative allergens identified in this search were not potent, common allergens, nor were any of them known to be allergenic when ingested. Moreover, comparison of the same *Pichia pastoris* proteins with all proteins in the NCBI Protein database identified far more significant matches to proteins found in commonly consumed fungi, including baker's yeast (*Saccharomyces* species). Thus, the bioinformatics searches did not reveal any similarities of concern between soy leghemoglobin and the 17 Pichia proteins and known allergens.

Dr. Goodman also tested the stability of LegH Prep in a model simulated gastric digestion study using the conditions recommended by Ofori-Anti et al. (Ofori-Anti, Ariyarathna, Chen, Lee, Pramod, & Goodman, 2008) to evaluate the pepsin stability of novel proteins in genetically modified crops. A positive correlation exists between the stability of abundant dietary proteins in this assay and the likelihood that they will be identified as food allergens. LegH Prep was very rapidly digested by pepsin (90% in less than 2 min). No stable protein fragments were detected either. On the basis of resistance to pepsin digestion, LegH Prep shows a low potential risk of allergenicity or toxicity.

Dr. Goodman stated "My conclusion from this "weight of evidence" approach to dietary protein safety is that the LegH Prep is very unlikely to present a risk of dietary allergy or toxicity to consumers."

Conclusions

We, members of the Expert Panel, have individually and collectively critically evaluated the information and data summarized above and other information deemed pertinent to the safety of the proposed uses of Soy Leghemoglobin Protein Preparation (LegH Prep). We unanimously conclude that the proposed uses as a protein component in ground beef replacement (analogue) products of LegH Prep, produced consistent with current Good Manufacturing Practice (cGMP) and meeting the appropriate food grade specifications presented above, are safe and suitable.

We unanimously conclude that the proposed uses as a protein component in ground beef replacement (analogue) products of LegH Prep, produced consistent with current Good Manufacturing Practice (cGMP) and meeting the food grade specifications presented above, are Generally Recognized As Safe (GRAS) based on scientific procedures.

It is our unanimous opinion that other qualified experts would concur with these conclusions.

(b) (6) [redacted]

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09 August 2017
Date

Michael W. Pariza, Ph.D.

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(b) (6) [redacted]

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6.7 Basis for GRAS Conclusion

Impossible Foods convened a panel of independent scientists (Expert Panel), qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, to conduct an independent, critical and comprehensive evaluation of the available safety information on its soy leghemoglobin protein preparation (LegH Prep), and to determine if the proposed use of soy leghemoglobin as a protein component in ground beef analogue products would be Generally Recognized as Safe (GRAS) based on scientific procedures.

In June 2017, the Expert Panel, independently and collectively, critically evaluated the documents provided by Impossible Foods and other information deemed appropriate or necessary including information pertaining to the method of manufacture, product specifications, batch analyses, intended levels of use, exposure estimates, and available scientific information pertaining to the safety of soy leghemoglobin and other plant and animal hemoglobins.

The Expert Panel reviewed reports prepared by Dr. Richard E. Goodman (Food Allergy Resource and Research Program (FARRP) of the University of Nebraska) that assessed the potential allergenicity and toxicity of LegH Prep, consistent with the Codex recommendations. Dr. Goodman conducted a comprehensive search of the biomedical literature to identify any published reports regarding possible allergenicity or toxicity associated with soy leghemoglobin and *Pichia pastoris* proteins and any reports regarding health issues associated with human consumption of soy leghemoglobin and *Pichia pastoris* proteins. Dr. Goodman concluded that there is no published evidence that soy leghemoglobin or the *Pichia pastoris* proteins present in LegH Prep were associated with allergic reactions or toxicity.

Dr. Goodman conducted bioinformatics searches (amino acid sequence comparisons) that compared the known sequence of soy leghemoglobin (GI:126241), as well as the *Pichia* proteins that are greater than or equal to 1% of the total protein fraction in LegH Prep, with known or putative allergens. The bioinformatics searches did not reveal any similarities of concern between soy leghemoglobin or the *Pichia* proteins and known allergens. Bioinformatics searches also were conducted to determine if similarities existed between the amino acid sequence of soy leghemoglobin and the *Pichia* proteins and the sequences of known toxic proteins. The search results did not raise concerns of potential toxicity for soy leghemoglobin or the *Pichia* proteins present in LegH Prep.

Additionally, Dr. Goodman's laboratory tested the stability of LegH Prep in a model simulated gastric digestion study using the conditions recommended by Ofori-Anti et al. (Ofori-Anti, Ariyarathna, Chen, Lee, Pramod, & Goodman, 2008) to evaluate the pepsin stability of novel proteins in genetically modified crops. The soy leghemoglobin and the *Pichia pastoris* proteins present in the preparation were very rapidly digested by pepsin. On the basis of resistance to pepsin digestion, LegH Prep (which includes soy leghemoglobin, *Pichia* proteins as well as other components; *see* Table 1), shows a low potential risk of allergenicity or toxicity.

Impossible Foods commissioned a bacterial reverse mutation (Ames) test and an *in vitro* mammalian chromosomal aberration test using human lymphocytes to evaluate the genotoxic potential of LegH Prep. These studies demonstrated that LegH Prep was neither mutagenic in bacterial cells nor clastogenic in human cells.

Impossible Foods commissioned a 28-day GLP feeding study in rats using the LegH Prep (containing soy leghemoglobin, *Pichia* proteins as well as other components; *see* Table 1) to determine the NOAEL for soy leghemoglobin with a max dose of 750 mg/kg/day soy leghemoglobin (43166). There were no clinically significant differences between groups in clinical observations, body weights, hematological parameters, clotting potential, or biochemical composition of the blood for both sexes. Therefore, the NOAEL for male and female rats was determined to be 750 mg/kg/day soy leghemoglobin. This represents a 112-fold safety factor above the 90th percentile EDI of 6.67 mg/kg/day soy leghemoglobin.

This weight of evidence approach to the safety assessment of soy leghemoglobin expressed in *Pichia pastoris* demonstrates that the LegH Prep (which contains soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1), is highly unlikely to present a dietary safety risk to consumers.

Following its independent and collective evaluation of the available information, the Expert Panel unanimously concluded that the intended use of soy leghemoglobin protein preparation (LegH Prep) as an ingredient in ground beef analogue products, manufactured consistent with current Good Manufacture Practice (cGMP) and meeting the food grade specifications presented in this notification is generally recognized as safe based on scientific procedures.

PART 7: LIST OF REFERENCES

Pursuant to 21 C.F.R. 170.255, the list of supporting data and information referenced in the GRAS notice is contained below.

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LIST OF ANNEXES

Annex 1

The globin structural superfamily is a large, well studied family of globular proteins, present in all domains of life: archae, bacteria, and eukaryotes (PFAM PF00042). All members of the globin structural superfamily are thought to share a common ancestor (Punta et al. 2012). The globin structural fold is comprised of eight alpha helical segments and a heme co-factor, which coordinates binding and/or transfer of oxygen. Structural comparisons of animal myoglobin, plant leghemoglobin, and plant non-symbiotic hemoglobin monomers are shown in Figure 1A-H. The crystal structure for cow myoglobin does not exist, so we have included myoglobin structures from tuna, pig, and horse in this analysis. Based on their similarity to eachother (Figure 1F-H), we expect that they are highly similar to cow myoglobin. The crystal structures were superimposed over all backbone atoms using the Super algorithm in PyMOL (Delano, 2007) (Figure 1I-L) and the corresponding root mean square deviations (RMSDs) are shown in Table 1 . Comparison of proteins folds (Figure 1) and RMSD values (Table 1) illustrates that animal myoglobins, plant non-symbiotic hemoglobins, and plant leghemoglobins all adopt the same globin fold and are structurally very similar. Furthermore, animal myoglobins, plant non-symbiotic hemoglobins, and plant leghemoglobins all bind the identical heme prosthetic group, heme B (Figure 1M).

The minimum temperature of denaturation for soy leghemoglobin, determined by Impossible Foods using dynamic light scattering, is 64 degrees Celsius (Figure 2A). Dynamic light scattering measures the mean effective diameter (Stokes radius) of a protein as a function of temperature. Increased Stokes radius indicates protein denaturation and aggregation. Protein denaturation leads to dissociation of the protein polypeptide from the heme co-factor. The denaturation temperature for soy leghemoglobin is similar to equine myoglobin, which Impossible Foods determined to be 70 degrees Celsius using dynamic light scattering. Lysozyme was included as a control and displayed the expected denaturation temperature of 72 degrees Celsius. The denaturation temperature for bovine myoglobin is 74 degrees Celsius (Sepe et al. 2005). The USDA recommended cooking temperature for ground beef is 160 degrees Fahrenheit (71 degrees Celsius). Impossible Foods' meat analogue is cooked at a similar temperature. Therefore, both mammalian myoglobins and leghemoglobin are denatured when consumed in a cooked meat or meat analogue product, respectively.

Proteins within the globin family typically denature and dissociate from their heme co-factor at pH <4. For example, at pH 3.2, human myoglobin dissociates from its heme co-factor in 45 seconds (Konermann et al 1997). To monitor heme-binding of the leghemoglobin polypeptide as a function of pH, Impossible Foods monitored the absorption spectra of the Soret region (Figure 2B). At pH 7, the heme co-factor is bound to the folded leghemoglobin polypeptide, as indicated by the narrow Soret peak at ~415 nm. At pH 2, the heme co-factor has dissociated from the denatured polypeptide, as indicated by the broad Soret peak at ~380 nm. Therefore, even if consumed in a raw meat analogue product, leghemoglobin will denature and release the heme co-factor upon exposure to the low pH environment of gastric fluid.

Leghemoglobins, non-symbiotic hemoglobins, and myoglobins each contain the identical heme b co-factor (Figure 1M). Soybean leghemoglobin does not contain peptide sequences that are associated with allergenicity (Annex 8), denatures at 64 degrees Celsius (Figure 2A) and pH 2 (Figure 2B), and is completely digested by pepsin (Annex 10), leaving only the heme cofactor. Therefore, the health effects of ingesting soybean leghemoglobin should be equivalent to non-symbiotic plant hemoglobins and mammalian myoglobins, which are readily consumed in the diet.

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Figure 1. Plant hemoglobins and animal myoglobins adopt the same structural fold. Individual plant leghemoglobins (A-B), plant non-symbiotic hemoglobins (C-E), and animal myoglobins (F-H), are shown in ribbon representation colored in gray, heme porphyrin ring is shown in red stick representation, and iron in blue CPK representation. Superposition of individual proteins shows that the 3D structure of soybean leghemoglobin is highly similar leghemoglobins, non-symbiotic hemoglobins, and myoglobins from different species (I-L).

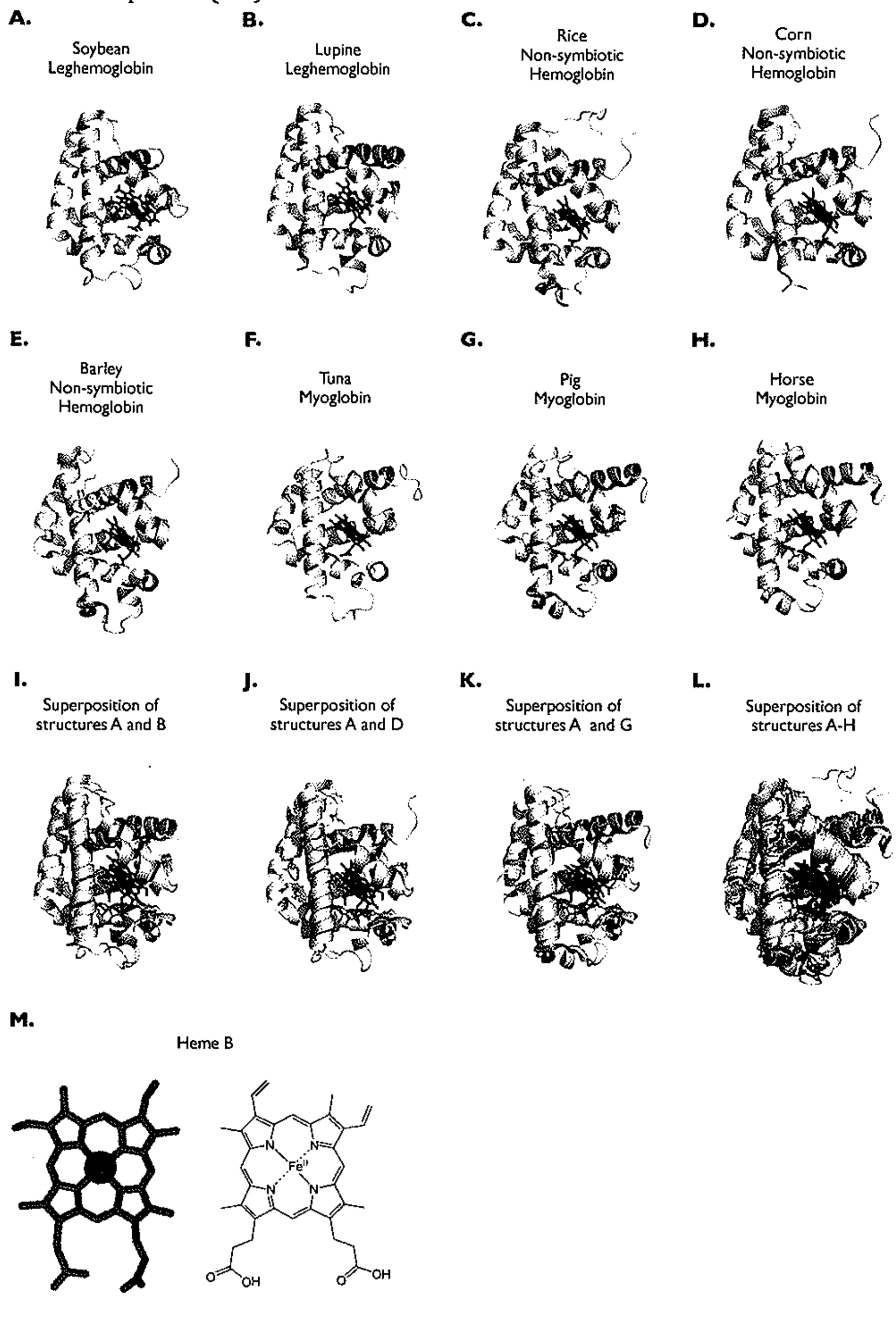
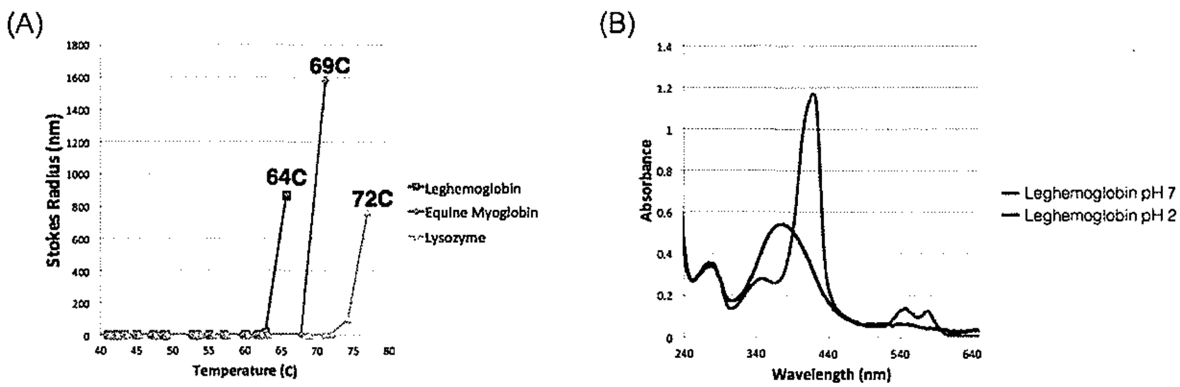


Table 1. Structural comparison between plant hemoglobins and animal myoglobins. Root-mean-square-deviation (RMSD) between all backbone atoms of superimposed X-ray crystallography protein structures (respective PDB codes are shown in parenthesis).

Species		RMSD (Å)
Soybean leghemoglobin (1BIN)	Horse myoglobin (1YMB)	4.5
Soybean leghemoglobin (1BIN)	Pig myoglobin (1PMB)	4.4
Soybean leghemoglobin (1BIN)	Tuna myoglobin (1MYT)	3.6
Soybean leghemoglobin (1BIN)	Barley non-symbiotic hemoglobin (2OIF)	2.5
Soybean leghemoglobin (1BIN)	Corn non-symbiotic hemoglobin (2R50)	1.0
Soybean leghemoglobin (1BIN)	Rice non-symbiotic hemoglobin (1D8U)	1.0
Soybean leghemoglobin (1BIN)	Lupine leghemoglobin (2GDM)	0.8
Soybean leghemoglobin (1BIN)	Soybean leghemoglobin (1FSL)	0.5

Figure 2. Leghemoglobin sensitivity to temperature and pH. (A) Impossible Foods measured the melting temperature of leghemoglobin using dynamic light scattering. Equine myoglobin (Sigma, cat# M0360) and Lysozyme (Sigma, cat# L4919) were included as controls. (B) Impossible Foods monitored heme dissociation from leghemoglobin at low pH by measuring the absorption spectra of the Soret region.



Annex 2

SOY LEGHEMOGLOBIN PREPARATION: A 28-DAY DIETARY STUDY IN RATS

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

DATA REQUIREMENT

OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Test No. 407): Health Effects, Repeated Dose 28-day Oral Toxicity Study in Rodents (2008)

US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. (2007)

STUDY NUMBER

43166

PERFORMING LABORATORY

Product Safety Labs
2394 US Highway 130
Dayton, New Jersey 08810

STUDY COMPLETION DATE

July 26, 2017

STUDY DIRECTOR

Mithila Shitut, BVSc & AH, MS

SPONSOR

Impossible Foods Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Soy Leghemoglobin Preparation

This study meets the requirements of US FDA GLP: 21 CFR Part 58, 1987 and OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998. Specific information related to the characterization of the test substance(s) as received and tested is the responsibility of the study sponsor (Section 3.B) with the following exception:

1) Chemistry analysis was not conducted in compliance with GLP regulations

Specific information related to the characterization of the test substance as received and tested is the responsibility of the study Sponsor (Section 3.A).

(b) (6)

Study Director: [redacted] Date: 7/26/17

Name of Signer: Mithila Shitut, BVSc & AH, MS

Name of Company: Product Safety Labs

(b) (6)

Sponsor: [redacted] Date: 7/26/17

Name of Signer: Rachel Fraser, PhD

Name of Company: Impossible Foods Inc.

(b) (6)

Submitter [redacted] Date: 7/26/17

Name of Signer: Rachel Fraser, PhD

Name of Company: Impossible Foods Inc.

QUALITY ASSURANCE STATEMENT

The Product Safety Labs' Quality Assurance (QA) Unit has reviewed this final study report to assure the report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study.

QA Activities for This Study:

QA Activity	Performed By	Date Conducted	Date Findings Reported To Study Director And Management
Protocol review	R. Krick; M. Zakrzewski	Sep 14, 2016; Nov 7 & 8, 2016	Sep 14, 2016; Nov 8, 2016
In-process inspection: *Study Schedule*	M. Zakrzewski	Sep 27, 2016	Sep 27, 2016
In-process inspection: *Diet Preparation and Sampling*	M. Zakrzewski	Sep 28, 2016	Sep 28, 2016
In-process inspection: *In-life and detailed observations*	M. Zakrzewski	Oct 19, 2016	Oct 19, 2016
In-process inspection: *Necropsy*	M. Zakrzewski	Oct 27, 2016	Oct 27, 2016
Raw data audit	M. Zakrzewski	Nov 7 & 8, 2016	Nov 8, 2016
Draft report review	M. Zakrzewski	Dec 16, 2016	Dec 16, 2016

QA Statements for the chemical analysis, clinical pathology and histopathology phases of the study may be found in Appendices D, N, and T, respectively.

Final report reviewed by:

(b) (6)

July 24, 2017
Date

Maryann Zakrzewski
Quality Assurance Auditor
Product Safety Labs

CERTIFICATION

We, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

(b) (6) [redacted]

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

26 July 2017
Date

(b) (6) [redacted]

Odete Mendes, DVM, PhD, DACVP, DABT
Director of Toxicology and Pathology
Product Safety Labs

26-July 2017
Date

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LIST OF TABLES

LIST OF APPENDICES

STUDY INFORMATION

Protocol No.:	P703.01 IMP
Test Substance(s):	Soy Leghemoglobin Preparation Lot #: PP-PGM2-16-088-301
Physical Descriptions:	Red/brown powder
Date Test Substance Received:	July 20, 2016
PSL IDs:	160720-5R
PSL Study Number:	43166
Sponsor:	Impossible Foods Inc. 525 Chesapeake Dr. Redwood City, CA 94063
Study Initiated-Completed:	September 21, 2016 – (see report cover page)
In-Life Study Initiated-Completed:	September 28 – October 28, 2016
Notebook No.:	16-43166: pages 1-466

KEY PERSONNEL

Product Safety Labs:

President:	Daniel J. Merkel, BS, MBA
Director of Toxicology and Pathology:	Odete Mendes, DVM, PhD, DACVP, DABT
Study Director:	Mithila Shitut, BVSc & AH, MS
Primary Scientist:	Colleen Wojenski, BS, LATG
Contributing Personnel:	Joshua Battaglia, BS Aubrey Blue Cynthia Bodnar Lisa Broske-Godin, BS, RLATG Stephanie DeCarlo, BS Janet Dell John, BA, RLATG Kathleen Quinn, BS Matthew Notta, BS Mark Schooley Matthew Sorber, BS Shannon Stevens, BS, CVT
Director of Quality Assurance:	Rhonda S. Krick, BS
Technical Writing Supervisor:	Celeste Dunn, AS

The following individual was responsible for the ophthalmology evaluations:

Ophthalmologist:	Kristina R. Vygantas, DVM, DACVO 319 Perrineville Road Robbinsville, NJ 08691

The following facility was responsible for the conduct and reporting of analysis of the neat test substance and all dietary preparations:

Test Substance and Dietary Analysis:	Impossible Foods Inc 525 Chesapeake Dr. Redwood City, CA 94063
Principal Investigator:	Rachel Fraser, PhD

KEY PERSONNEL (cont.)

The following were responsible for the clinical pathology analysis:

Clinical chemistry, hematology, coagulation and urinalysis:	DuPont Haskell Global Centers for Health and Environmental Sciences P.O. Box 30, Elkton Road Newark, Delaware 19714
Principal Investigator:	Denise Hoban, BA, MLT, ASCP
Clinical pathology evaluations:	Product Safety Labs 2394 US Highway 130 Dayton, New Jersey 08810
Principal Investigator:	Odete Mendes, DVM, PhD, DACVP, DABT

The following were responsible for the histological slide preparation and pathology evaluations:

Histological slides preparation:	HSRL Histo-Scientific Research Laboratories 5930 Main Street Mount Jackson, VA 22842
Histology Principal Investigator:	Craig Zook
Histological slide evaluation by:	HSRL Histo-Scientific Research Laboratories 5930 Main Street Mount Jackson, VA 22842
Pathology Principal Investigator:	Daniel G. Branstetter, DVM, PhD, DACVP
Histopathology Peer Review	Regan Path/Tox Services, Inc, 1457 Township Road 853 Ashland, OH 44805 P.I. (pathology): Karen Regan, DVM, DABT, DACVP

1. OBJECTIVE

The objective of this study was to evaluate the potential subchronic toxicity of Soy Leghemoglobin Preparation in male and female rats likely to arise from continuous exposure to the test substance in the diet for at least 28 days. A no-observed-adverse-effect-level (NOAEL) was also sought for each sex.

2. SUMMARY

A 28-day dietary toxicity study was conducted in Crl:SD CD® IGS rats to determine the potential of Soy Leghemoglobin Preparation to produce toxicity. Eighty (80) healthy rats (40 males and 40 females) were selected for the test and equally distributed into four groups (10/sex/group). Dietary test substance levels 512, 1024 and 1536 mg/kg/day corresponded to 250 mg/kg/day (Group 2), and 500 mg/kg/day (Group 3), and 750 mg/kg/day (Group 4) of active ingredient, as well as a Basal diet control (Group 1), were evaluated.

The neat test substance was measured to be stable under the conditions of storage over the course of this study. Stability of test substance in the diet was evaluated by analyzing the low, medium, and high dietary concentrations of the test substance on Days 0, 4, 7, and 10 following preparation. Test substance homogeneity in the diet was assessed at the beginning of the study by evaluating the low, medium, and high dietary levels in the top, middle, and bottom strata of the diet preparations. At the beginning, middle, and end of the study, selected diet preparation samples were analyzed to verify test substance concentration in the diets over the course of the study. Results from the homogeneity, stability, and concentration analyses of the test diets indicate that Soy Leghemoglobin Preparation was homogeneously distributed within an acceptable margin of variability, stable in the dietary matrix, and was considered to have met target concentrations in the diet for all intake levels.

The animals were examined by focal illumination and indirect ophthalmoscopy prior to initiation and again at the end of the study (Day 23), observed for viability, signs of gross toxicity and behavioral changes at least once daily during the study and weekly for a battery of detailed clinical observations. Body weight and food consumption measurements were collected throughout the study and used to calculate the mean overall daily intake of test substance. Urine and blood samples were collected on Day 22 from all study animals for urinalysis, hematology and clinical chemistry determinations. Gross necropsies and histological evaluation of selected organs and tissues were performed on all study animals.

Administered doses of 512, 1024 and 1536 mg/kg/day of test substance correspond to 250, 500 and 750 mg/kg/day of the active, respectively. The mean overall (Days 0-28) daily intake of the test substance in male rats fed dietary concentrations of 512, 1024 and 1536 mg/kg/day was 478.9, 954.7 and 1438.2 mg/kg/day respectivelly. For the same dietary concentrations, the mean overall (Days 0-28) daily intake in female rats was 497.8, 983.4, and 1470.4 mg/kg/day of test substance, respectively. The animals are considered to have received close to the targeted dose levels.

There were no mortalities, clinical observations, ophthalmology, body weight, body weight gain, food consumption, or food efficiency changes attributable to Soy Leghemoglobin Preparation administration.

There were no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or females rats. Changes in coagulation paramentes were limited to a non dose-dependent increase in activated partial tromboplastin time observed in Group 3 and 4 males,

that due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non adverse.

There were no microscopic or macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

Under the conditions of the study and based on the toxicological endpoints evaluated, the no-adverse-effect level (NOAEL) for administration of Soy Leghemoglobin Preparation in the diet was determined to be 1536 mg/kg/day, which corresponds to 750 mg/kg/day of the active ingredient Soy Leghemoglobin for Sprague Dawley rats.

3. TEST SUBSTANCE

A. Source

The test substance was provided by the Sponsor.

B. Identification

The test substance was received on July 20, 2016, and identified using the following information provided by the Sponsor and Product Safety Labs (PSL) identification number.

Test Substance: Soy Leghemoglobin Preparation
PSL ID: 160720-5R
Lot #: PP-PGM2-16-088-301
Physical Description: Red/brown powder
Composition: Soy Leghemoglobin 48.82%
Storage Conditions: Frozen
Expiration Date: Not Applicable

Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

C. Analysis

The test substance, as received, was expected to be stable for the duration of the study. Stability of the neat test substance in the dietary matrix and that of the concentration of the test substance in the test diets was determined as part of this study.

D. Hazards

Appropriate routine safety precautions were exercised in the handling of the test and control substances.

4. GENERAL TEST SYSTEM PARAMETERS

A. Animal Requirements

4.A.1 Number of Animals: 80

4.A.2 Number of Groups: 4 (3 dietary levels per sex + 1 control group per sex)

4.A.3 Number of Animals per Group: 20 (10 male, 10 female)

4.A.4 Sex: Male and female; females will be nulliparous and non-pregnant.

4.A.5 Species/Strain: CRL Sprague-Dawley CD® IGS rats

4.A.6 Age/Weight: Seven to eight weeks at initiation; the weight variation did not exceed ± 20% of the mean weight for each sex.

4.A.7 Supplier: Charles River Laboratories, Inc. Rats were shipped in filtered cartons by airfreight and/or truck.

On September 22, 2016, 88 CRL Sprague-Dawley CD® IGS rats (44 males and 44 females) arrived from Charles River Laboratories, Inc., with an assigned birth date of August 6, 2016. The rats were designated by the supplier to be 6-7 weeks of age upon arrival.

B. Test System Justification

The Sprague-Dawley® rat was the system of choice because, historically, it has been a preferred and commonly used species for dietary toxicity tests. The current state of scientific knowledge does not provide acceptable alternatives to the use of live animals to accomplish the objective of this study.

C. Animal Husbandry

4.C.1 Housing

The animals were group housed in suspended stainless steel caging, which conforms to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals* (Natl. Res. Council, 2011). Litter paper was placed beneath the cages and was changed at least three times per week. The animal room had a 12-hour light/dark cycle and was kept clean and vermin free.

4.C.2 Animal Room Temperature and Relative Humidity Ranges

The animal room was temperature and humidity were 19-23°C and 39-62%, respectively.

4.C.3 Acclimation

The animals were conditioned to the housing facilities for six days prior to testing. Body weights and clinical observations were recorded at least two times prior to study start.

4.C.4 Feed

2016 certified Envigo Teklad Global Rodent Diet® was stored in a dedicated temperature and humidity monitored feed storage site and was available *ad libitum* during acclimation. Test diets were prepared as described in Section 6.B using 2016 certified Envigo Teklad Global Rodent Diet® and were available *ad libitum* during the study.

4.C.5 Water

Filtered tap water was available *ad libitum*. Water analysis was conducted by Precision Analytical Services, Inc., Toms River, NJ and South Brunswick Municipal Water Supply, South Brunswick, NJ.

4.C.6 Contaminants

There were no known contaminants reasonably expected to be found in the food or water that would interfere with the results of this study. Routine analysis consisting of each lot of feed used in this study was received from Envigo Teklad, Madison, WI. Water analysis was conducted periodically and the records are kept on file at Product Safety Labs. The date(s) of the most recent analyses are reported in Appendix B.

4.C.7 Viral Screen

The animals used in this study were considered to be pathogen-free as received from the vendor (Section 4.A.). Rodent-health surveillance for study animals was monitored by designating three rats as "sentinels" for the study room (Animals 257M 10.28.16, 268M 10.28.16, and 316F 10.28.16). Sentinels were housed under the conditions of the study, on racks alongside study animals, for the duration of the study (September 28 – October 28, 2016). These animals were not a part of the study, and were clearly marked as such. A serum sample was collected from each sentinel rat for screening of common rat pathogens (Rat Parvovirus, Toolan's H-1 Virus, Kilham Rat Virus, Rat Minute Virus, Parvovirus NS-1, Rat Coronavirus, Rat Theilovirus, and Pneumocystis carinii). The serum samples were sent on ice to IDEXX BioResearch (Columbia, MO) for evaluation. Serological pathogen screening results for the sentinels 257M 10.28.16, 268M 10.28.16, and 316F 10.28.16, corresponding with this study, are reported in Appendix B. The sentinel samples were negative for all pathogens evaluated and therefore, the study animals were considered to be healthy and reasonably free of common rat pathogens.

D. Identification

4.D.1 Cage

Each cage was identified by a cage card indicating the study number, dose level, group assignment, individual animal identification and sex of the animal.

4.D.2 Animal

Each animal was given a sequential number in addition to being uniquely identified with a Monel® self-piercing stainless steel ear tag.

5. EXPERIMENTAL DESIGN

A. Route of Administration

The test substance was administered in the diet.

B. Justification of Route of Administration

The dietary route of administration was used because it was recommended in the referenced guidelines (Section 8.C.), as human exposure may occur via this route.

C. Control of Bias

Animals were randomly assigned to test groups, stratified by body weight.

D. Dose Levels

Ten male and ten female test animals were randomly assigned to each of the following test groups:

Group	No. Animals/ Group M/F	Dietary Dose Level/ Target Exposure of Active Ingredient (mg/kg/day)	Dietary Dose Level/ Target Exposure of Test Substance [a] (mg/kg/day)
1	10/10	0	0
2	10/10	250	512
3	10/10	500	1024
4	10/10	750	1536

[a] Based on 48.82% active ingredient (AI, Soy Leghemoglobin) of Soy Leghemoglobin Preparationlot # PP-PGM2-16-088-301

E. Justification of Dose Level Selection

The Sponsor, in consultation with the Study Director, and based on a 14-day palatability/toxicity study (PSL, 2016) selected target dietary dose levels of 512, 1024 and 1536 mg/kg/day that correspond to target dose levels of 250, 500 and 750 mg/kg/day of the active ingredient, Soy leghemoglobin. To maintain target dietary dose levels throughout the study, concentrations in the test diets were calculated based on the most recent group body weight and food consumption data. Alternatively, historical control values, relevant to the age and weight of the rats at corresponding intervals were used. Diets for males and females at each dietary dose level were made separately each week. A NOAEL was expected to be achieved for this study.

6. GENERAL PROCEDURES

A. Selection of Animals

After acclimating to the laboratory environment for 6 days, the rats were examined for general health and weighed. Only those rats free of clinical signs of disease or injury and having a body weight range within ±20% of the mean were selected for test. Eighty (80) healthy rats (40 males; 40 females) were selected for test. The animals weighed 227-250 grams (males) and 156-198 grams (females) and were approximately 7-8 weeks of age at initiation of dosing. The rats that were used on test were randomly distributed, stratified by body weight, among the dose and control groups on the day of study start.

B. Diet Preparation and Sampling

6.B.1 Diet Preparation

The test substance was processed as needed to decrease particle size using a grinder and then added to 2016 Envigo Teklad Global Rodent Diet® and thoroughly mixed in a high-speed mixer. Control diet was mixed under the same conditions as the diets prepared with the test substance. All diets were kept frozen following preparation, unless presented to the test animals on the same day as diet preparation. All diets were prepared approximately weekly.

6.B.2 Diet Presentation

The control and test diets were presented to their respective groups on Day 0 of the study. The diets were replaced concurrently with food consumption measurements on Days 3, 7, 10, 14, 17, 21 and 24. Additional diet may be provided as needed throughout the study to insure *ad libitum* feeding. Animals were exposed to the test diets for at least 28 days.

6.B.3 Sampling

The neat test substance and selected prepared diets (at each concentration) were sampled in duplicate.

6.B.4 Stability of Test Substance

At the initial, middle, and final diet preparation, a sample of the test substance (neat) was retained for stability. Analytical results of the initial and final stability samples were used to establish the stability of the test substance under normal laboratory conditions for the duration of the study.

6.B.5 Stability in Dietary Matrix

During the first week of the study, samples to verify the stability of the test and control substance in the dietary matrix were prepared. Samples were prepared in standard feed jars with followers and retaining rings and were stored at ambient temperature in the animal room. Samples from each dietary concentration were collected at the first presentation of the diet and after 4, 7, and 10 days and frozen until analyzed.

6.B.6 Homogeneity

Samples to evaluate homogeneity of the test and control substance distribution were collected from the initial diet preparation. Samples were taken from approximately the top, middle and bottom of the diet mixer. Basal diet control samples were collected from the middle of the mixer only. Chemical analysis verified the diets as homogeneous and of accurate concentration throughout the study.

6.B.7 Concentration Verification

Samples were collected from representative animal diets of the initial (as part of the homogeneity assessment), middle and final diet preparations during which time samples were retained and stored frozen. Samples were analyzed to verify the concentration of the test diets.

6.B.8 Sample Preservation

Upon sampling, diet preparations and neat test substance were stored frozen. Samples were considered stable from the point at which they were frozen.

6.B.9 Sample Analysis

A single duplicate of the frozen diet samples described above was sent to Impossible Foods for analysis of diet preparation and neat test substance samples. A signed, analytical report was provided to the Study Director. This report included the methodology, pertinent measurements, study results, and tabulated results. Upon completion of the report, all raw data was transferred to the Study Director to be incorporated into the main study report. Any remaining sample material was retained at Product Safety Labs until issuance of the final report.

C. Ophthalmologic Evaluations

During the acclimation period, the eyes of all rats being considered for study were examined by focal illumination, indirect ophthalmoscopy and, when indicated, slit-lamp microscopy. Mydriatic eye drops were administered prior to ophthalmoscopy and the eyes were examined in subdued light. Subdued light was maintained in the animal room. These procedures were repeated on all test animals prior to test termination on Day 23.

D. Clinical Observations

All animals were observed at least twice daily for viability. Cage-side observations of all animals were performed daily during the study. All findings were recorded.

On Day 0, prior to the first treatment with the test substance, and weekly thereafter, a detailed observation was conducted while handling the animal, generally on days that the animals were weighed and food consumption measurements were taken. Potential signs noted included, but were not limited to: changes in skin, fur, eyes, and mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Likewise, changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies (e.g., excessive grooming, repetitive circling), or bizarre behavior (e.g., self-mutilation, walking backwards) were also recorded. The date and clock time of all observations and/or mortality checks were recorded.

E. Body Weight and Body Weight Gain

Individual body weights were recorded twice during acclimation. Test animals were weighed on Day 0 (prior to study start) and weekly thereafter (intervals of 7 days ± 1). The animals were also weighed prior to sacrifice in order to calculate organ-to-body weight ratios (Amendment 1). Body weight gain was calculated for selected intervals and for the study overall.

F. Food Consumption, Food Efficiency, and Dietary Intake of Soy Leghemoglobin Preparation

Individual food consumption was measured and recorded on Days 3, 7, 10, 14, 17, 21, 24 and at the end of the study. Food efficiency and dietary intake of the test substance (mg/kg/day) was also calculated and reported.

G. Clinical Pathology

Clinical pathology was performed on all animals for blood chemistry and hematology of the terminal sacrifice animals at the end of the dosing phase of the study. The animals were fasted overnight prior to blood collection. Blood samples for hematology (except coagulation samples) and clinical chemistry were collected via sublingual bleeding under isoflurane anesthesia during Week 4 of the test period. Approximately 500 µL of blood was collected in a pre-calibrated tube containing K_2EDTA for hematology assessments. The whole blood samples were stored under refrigeration and shipped on cold packs. Approximately 1000 µL of blood was collected into a tube containing no preservative for clinical chemistry assessments. These samples were centrifuged in a refrigerated centrifuge and the serum was transferred to a labeled tube. Serum samples were stored in a -80°C freezer and shipped frozen on dry ice. All samples were shipped to DuPont Haskell Global Centers for Health and Environmental Sciences.

The day before collection of samples for the clinical pathology evaluation, the animals were placed in metabolism cages. Animals were fasted after 3 pm (at least 15 hours prior to) and urine was collected from each animal. Urine samples were stored under refrigeration and shipped on wet ice to DuPont Haskell Global Centers for Health and Environmental Sciences.

Blood samples used to determine the prothrombin time and activated partial thromboplastin time (coagulation) were collected via the inferior vena cava under isoflurane anesthesia at terminal sacrifice. Approximately 1.8 mL of blood was collected in a pre-calibrated tube containing 3.2% sodium citrate. These samples were centrifuged in a refrigerated centrifuge and the plasma was transferred to labeled tubes. Plasma samples were stored in a -80° C freezer and shipped frozen in dry ice to DuPont Haskell Global Centers for Health and Environmental Sciences. In addition, a second blood sample was retained during the exsanguination procedure for future possible evaluation.

All blood samples were evaluated for quality by visual examination.

6.G.1 Hematology included:

erythrocyte count (RBC)	hemoglobin concentration (HGB)
hematocrit (HCT)	mean corpuscular volume (MCV)
mean corpuscular hemoglobin (MCH)	red cell distribution width (RDW)
absolute reticulocyte count (ARET)	platelet count (PLT)

total white blood cell (WBC) and differential leukocyte count

Mean corpuscular hemoglobin concentration (MCHC) was calculated.

In addition, separate, blood smears, stained with New Methylene Blue or Wright-Giemsa stain, were prepared from each animal undergoing hematological evaluation, but were not needed for examination.

6.G.2 Coagulation included:

prothrombin time (PT)
activated partial thromboplastin time (APTT)

6.G.3 Clinical chemistry included:

serum aspartate aminotransferase (AST)	serum alanine aminotransferase (ALT)
sorbitol dehydrogenase (SDH)	alkaline phosphatase (ALKP)
total bilirubin (BILI)	urea nitrogen (BUN)
blood creatinine (CREA)	total cholesterol (CHOL)
triglycerides (TRIG)	fasting glucose (GLUC)
total serum protein (TP)	albumin (ALB)
globulin (GLOB)	calcium (CALC)
inorganic phosphorus (IPHS)	sodium (NA)
potassium (K)	chloride (CL)

6.G.4 Urinalysis included:

quality (QUAL)	pH	ketone (KET)
color (COL)	glucose (UGLC)	bilirubin (UBIL)
clarity (CLAR)	specific gravity (SG)	blood (BLD)
volume (UVOL)	protein (UMTP)	urobilinogen (URO)

microscopic urine sediment examination

Any remaining serum samples were maintained frozen at approximately -80°C and discarded upon approval of the Sponsor at finalization.

H. Terminal Sacrifice and Histopathology

6.H.1 Scheduled Sacrifice

At terminal sacrifice, all survivors were euthanized by exsanguination from the abdominal aorta under isoflurane anesthesia. All animals in the study were subjected to a gross necropsy, which included examination of the external surface of the body, all orifices, musculoskeletal system, and the cranial, thoracic, abdominal, and pelvic cavities, with their associated organs and tissues. All gross lesions were recorded. The following tissues were weighed wet as soon as possible after dissection to avoid drying:

adrenals (combined)	kidneys (combined)	testes (combined)
brain	liver	thymus
epididymides (combined)	ovaries with oviducts (combined)	uterus
heart	spleen	

The following organs and tissues from all animals were preserved in 10% neutral buffered formalin for possible future histopathological examination:

accessory genital organs (prostate and seminal vesicles)	ileum with Peyer's patches	rectum
adrenals	jejunum	salivary glands (sublingual submandibular, and parotid)
all gross lesions	kidneys	skeletal muscle
aorta	larynx	skin
bone (femur)	liver	spinal cord – 3 levels: cervical, mid-thoracic, and lumbar
bone marrow (from femur & sternum)	lungs	spleen
brain – 3 sections including medulla/pons, cerebellar, and cerebral cortex	lymph node mandibular	sternum
cecum	lymph node mesenteric	stomach
cervix	mammary gland	thymus
colon	nasal turbinates	thyroid
duodenum	nose	trachea
esophagus	ovaries	urinary bladder
Harderian gland	oviducts	uterus
heart	pancreas	vagina
	parathyroid	
	peripheral nerve (sciatic)	
	pharynx	
	pituitary gland	

The following organs and tissues from all animals were preserved in modified Davidson's fixative and then stored in ethanol for possible future histopathological examination:

eyes	optic nerve
epididymides	testes

Additional tissues were preserved if indicated by signs of toxicity or target organ involvement.

6.H.2 Histopathology

Histological examination was performed on the preserved organs and tissues of the animals from both the control and high dose groups (Groups 1 and 4, respectively). The fixed tissues were trimmed, processed, embedded in paraffin, sectioned with a microtome, placed on glass microscope slides, stained with hematoxylin and eosin (HE) and examined by light microscopy. Additional special stains can be added based on HE evaluation at the discretion of the study pathologist in consultation with the study director and sponsor. Slide preparation and histological assessment, by a board-certified veterinary pathologist, was performed at Histo-Scientific Research Laboratories (HSRL).

6.H.3 Histopathology Peer Review

A histopathology peer review of female reproductive organs was performed for all female rats (Ammendment 3). The peer review pathologist was Karen Regan, DVM, DABT, DACVP form Regan Path/Tox Services, Inc, 1457 Township Road 853, Ashland, OH 44805. A peer review statement will be inserted in Appendix U.

7. STATISTICAL ANALYSIS

Product Safety Labs performed statistical analysis of all data collected during the in-life phase of the study as well as organ weight data. DuPont Haskell Global Centers for Health and Environmental Services provided analysis of clinical pathology results to Product Safety Labs. The use of the word "significant" or "significantly" indicates a statistically significant difference between the control and the experimental groups. Significance was judged at a probability value of $p<0.05$. Male and female rats were evaluated separately.

A. Statistical Methods (In-Life and Organ Weight Data)

Mean and standard deviations were calculated for all quantitative data. If warranted by sufficient group sizes, data within groups were evaluated for homogeneity of variances and normality by Bartlett's test (Bartlett, 1937). Where Bartlett's test indicated homogeneous variances, treated and control groups were compared using a one-way analysis of variance (ANOVA). When one-way analysis of variance was significant, a comparison of the treated groups to control by Dunnett's test (Dunnett, 1964, 1980) for multiple comparisons was performed. Where variances were considered significantly different by Bartlett's test, groups were compared using a non-parametric method (Kruskal-Wallis non-parametric analysis of variance; Kruskal and Wallis, 1952). When non-parametric analysis of variance was significant, comparison of treated groups to control was performed using Dunn's test (Dunn, 1964). Statistical analysis was performed on all quantitative data for in-life and organ weight parameters using Provantis® version 9, Tables and Statistics, Instem LSS, Staffordshire UK.

B. Statistical Methods (Clinical Pathology)

Significance was judged at a probability value of $p < 0.05$. Males and females were analyzed separately (Provantis™ version 8, Tables and Statistics, Instem LSS, Staffordshire UK).

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Clinical Pathology[a]	Levene's test for homogeneity and Shapiro-Wilk test for normality	One-way analysis of variance followed with Dunnett's test	Transforms of the data to achieve normality and variance homogeneity were used. The order of transforms attempted was log, square-root, and rank-order. If the log and square-root transforms failed, the rank-order was used.

[a] When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity was reported as >1.100, 1.100 is used for any calculation performed with that specific gravity data.

8. STUDY CONDUCT

A. Laboratory

In-life portion	Product Safety Labs 2394 US Highway 130 Dayton, NJ 08810
Ophthalmology evaluation	Kristina R. Vygantas, DVM, DACVO 319 Perrineville Rd. Robbinsville, NJ 08691
Clinical chemistry, hematology, coagulation, and urinalysis	Dupont Haskell Global Centers for Health and Environmental Sciences P.O. Box 30 Elkton Road Newark, DE 19714 P.I.: Denise Hoban, BA, MLT, ASCP
Clinical pathology evaluation	Product Safety Labs 2394 US Highway 130 Dayton, NJ 08810 P.I.: Odete Mendes, DVM, PhD, DACVP, DABT
Test substance and dietary analysis	Impossible Foods Inc 525 Chesapeake Dr. Redwood City, CA 94063 P.I.: Pavel Aronov, PhD
Histological slide preparation	Histo-Scientific Research Laboratories (HSRL) 5930 Main Street Mount Jackson, VA 22842 P.I. (histology): Craig Zook

Histological slide evaluation	Histo-Scientific Research Laboratories (HSRL) 5930 Main Street Mount Jackson, VA 22842 P.I. (pathology): Daniel G. Branstetter, DVM, PhD, DACVP
Histopathology Peer Review	Regan Path/Tox Services, Inc, 1457 Township Road 853 Ashland, OH 44805 P.I. (pathology): Karen Regan, DVM, DABT, DACVP

B. GLP Compliance

This study was conducted in compliance with the following regulations:

- U.S. FDA GLP: 21 CFR Part 58, 1987

Which is compatible with:

- OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

Clinical pathology assessment was conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Good Laboratory Practices.

Analysis of the neat test substance and test substance in the dietary matrix, for homogeneity, stability, and dose concentration verification, were performed in a non-GLP certified facility.

C. Test Procedure Guidelines

This study design was based on the following guidelines:

- OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Test No. 407): Health Effects, *Repeated Dose 28-day Oral Toxicity Study in Rodents* (2008).

- US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. (2007).

9. FINAL REPORT AND RECORDS TO BE MAINTAINED

The original, signed final report was sent to the Sponsor. A copy of the signed report, together with the protocol and all raw data generated at Product Safety Labs, will be maintained in the Product Safety Labs Archives. PSL will maintain these records for a period of at least five years. After this time, the Sponsor of the study will be offered the opportunity to take possession of the records or request continued archiving by PSL.

The following records are maintained:

A. Information on test substance includes but is not limited to the following:

Storage	Dietary analysis
Usage	Test substance analysis
Disposition	

B. Information on animals includes but is not limited to the following:

Receipt, date of birth	Clinical observations
Initial health assessment	Histopathology data
Dosing	Individual necropsy records
Body weights	Organ weights
Food consumption	Ophthalmologic evaluations

Hematology, clinical chemistry, coagulation, urinalysis data

All other records that would demonstrate adherence to the protocol.

Raw data related to hematology and clinical chemistry evaluations will be maintained by Product Safety Labs and/or DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, DE. Prepared slides and pathology data will be maintained by Product Safety Labs and/or by HSRL, 5930 Main Street, Mount Jackson, VA, 22842. Test substance and dietary analysis data will be maintained by Impossible Foods Inc. 525 Chesapeake Dr. Redwood City, CA 94063.

10. PROTOCOL AND PROTOCOL AMENDMENTS

See Appendix A for the Protocol and Protocol Amendments.

11. RESULTS

A. Test Substance and Diet Analysis (Table 1A-D, Appendix D)

The test substance was expected to be stable under the conditions of storage over the course of this study.

11.A.1 Analysis of Soy Leghemoglobin Preparation Neat Test Substance

Soy Leghemoglobin Preparation was found to be stable under the conditions of storage over the course of this study. Results of the stability analysis of Soy Leghemoglobin Preparation from Day 0 to Day 21, found a change of -4.30%, for an overall test substance stability of 95.70% over the course of the study, within the range of analytical variance of measured test substance.

11.A.2 Stability

Dietary stability samples collected after 10 days of storage were compared to the initial samples for overall in-room stability of the test substance in the dietary matrix. All dietary mixtures were found to be stable within an acceptable degree of variation. The results of the stability were 90.74, 96.65, and 97.77% and 99.63, 93.78, and 97.38% on Day 10 of the nominal concentrations of 250, 500, and 750 mg/kg/day Soy Leghemoglobin Preparation for Groups 2-4 males and females, respectively.

11.A.3 Homogeneity

A sampling from the top, middle, and bottom of the dietary preparations found all dietary mixtures to be homogeneously distributed within an acceptable degree of variation. Analysis of the top, middle, and bottom of the dietary preparations resulted in a relative standard deviation (RSD) of 2.92, 3.09, and 5.24% and 4.77, 5.50, and 5.57% between the strata, for concentrations of 512, 1024, and 1536 mg/kg/day Soy Leghemoglobin Preparation, which corresponds to 250, 500, and 750 mg/kg/day of active ingredient for Groups 2-4 males and females, respectively.

11.A.4 Concentration Verification

Concentration verification results for Day 0 (obtained from the homogeneity analysis) averaged 92.86, 93.13, and 103.35% and 97.28, 98.53, and 100.35% for 250, 500, and 750 mg/kg/day Soy Leghemoglobin Preparation for Groups 2-4 males and females, respectively. Day 21 resulted in 93.24, 97.05, and 94.73% and 92.80, 97.76, and 97.65% for 250, 500, and 750 mg/kg/day Soy Leghemoglobin Preparation for Groups 2-4 males and females, respectively.

Based on the stability, homogeneity, and dose concentration verification results, the animals are considered to have received the targeted dietary concentrations of Soy Leghemoglobin Preparation, with an acceptable margin of variability.

B. Ophthalmologic Examinations (Appendix E)

Both eyes of all animals on study were examined by focal illumination, slit lamp biomicroscopy, and indirect ophthalmoscopy prior to study initiation and near termination of the study (Day 23). All animals included in the study were normal upon ophthalmic exam. Therefore, the test substance was not considered an ocular toxicant.

C. Mortality and Clinical Observations (Tables 2 and 3, Appendices F-H, and O)

No mortalities were observed during this study. There were no clinical observations attributable to the administration of Soy Leghemoglobin Preparation.

Males

Incidental in-life clinical observations included: red staining in the litter tray of 7/10 Group 4 animals and superficial eschar of the head in 1/10 Group 4 animals.

There were no detailed clinical observations noted for any male during the study.

Females

Incidental in-life clinical observations included: slight to moderate alopecia on the left/right forelimb in 1/10 Group 2 animals.

Incidental detailed clinical observations corresponding to the daily findings included hair loss in 1/10 Group 2 animals.

The fate of all animals is presented in Appendix O.

D. Body Weight and Body Weight Gain (Tables 4 and 5, Appendices I and J)

There were no body weight or body weight gain findings considered attributable to Soy Leghemoglobin Preparation administration.

Males

Mean body weights and mean daily bodyweight gain for the treated male rats in Groups 2-4 were comparable to the control Group 1 values throughout the study.

Females

Mean body weights for the treated female rats in Groups 2-4 were comparable to the control Group 1 values throughout the study.

Mean daily body weight gain for the treated female rats in Groups 2-4 was generally comparable to the control Group 1 values throughout the study with the exception of a transient statistically significant decrease ($p < 0.01$) in Group 2 mean daily body weight gain on Days 14-21 that was interpreted to have no toxicological relevance.

E. Food Consumption, Food Efficiency, and Dietary Intake of Soy Leghemoglobin Preparation (Tables 6-8, Appendices K-M)

There were no food consumption or food efficiency findings considered attributable to Soy Leghemoglobin Preparation administration.

Males

Mean daily food consumption for the treated male rats in Group 2-4 was generally comparable to the control Group 1 values throughout the study with the exception of significant increases ($p <$ 0.05-0.01) in Group 3 on Days 7-14 and in Group 4 on Days 7-10, that we transient and without significant inpact on body weight and are interpreted to be non-toxicologically relevant

Mean food efficiency for the treated male rats in Group 2-4 was comparable to the control Group 1 values throughout the study.

Females

Mean daily food consumption for the treated female rats in Group 2-4 was comparable to the control Group 1 values throughout the study.

Mean food efficiency for the treated female rats in Group 2-4 was generally comparable to the control Group 1 values throughout the study, with the exception of statistically significant increases ($p < 0.01$) in Group 2 on Days 14-21 that were transient and without significant inpact on body weight and are interpreted to be non-toxicologically relevant.

Dietary Intake

Administered doses of 512, 1024 and 1536 mg/kg/day of test substance correspond to 250, 500 and 750 mg/kg/day of the active, respectively. The mean overall (Days 0-28) daily intake of the test substance in male rats fed dietary concentrations of 512, 1024 and 1536 mg/kg/day was 478.9, 954.7 and 1438.2 mg/kg/day respectivelly. For the same dietary concentrations, the mean overall (Days 0-28) daily intake in female rats was 497.8, 983.4, and 1470.4 mg/kg/day of test substance, respectively. The animals are considered to have received close to the targeted dose levels.

F. Clinical Pathology (Tables 9-12, Appendix N)

11.F.1 Hematology

There were to no test substance related changes in hematology parameters for males or females rats.

Other differences in hematology values that were statistically significant are listed below. These were observed in a non-dose dependent manner and are interpreted to be within expected biological variation and are not toxicologically relevant:

- Increased Red blood cell, hemarocrit and Hemoglobin values and absolute basophil counts in Group 2 females.
- Decreased absolute reticulocyte counts in Group 3 females.

11.F.2 Coagulation

There were no test substance related changes in coagulation parameters for female rats.

A non dose dependend increase in activated partial tromboplastin time was observed in Group 3 and 4 males. Due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non adverse.

11.F.3 Clinical Chemistry

There were no test substance related changes in serum chemistry parameters for male rats.

Decreased alkaline phosphatase was minimally decreased in a non dose dependent manner for females at all dose levels. This minimal decrease was not correlated with concurrent clinical pathology or histopathology changes and due to its limited clinical relevance is interpreted to have no toxicological significance.

Other differences in serum chemistry parameters that were statistically significant are listed below. These were observed in a non-dose dependent manner and are interpreted to be within expected biological variation and are not toxicologically relevant:

- Increased albumin and potassium values in Group 3 males.
- Decreased glucose and chloride in Groups 2 and 3 females.
- Increased globulin values in Group 3 females.
- Increased calcium in Groups 2 and 3 females.

11.F.4 Urinalysis

There were no test substance related changes in urinalysis parameters for males or female rats.

In summary, there were to no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or females rats. Changes in coagulation paramenters were limited to a non dose dependent increase in activated partial tromboplastin time observed in Group 3 and 4 males, that due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non-adverse.

G. Sacrifice, Macroscopic Observations, and Histopathology (Tables 13-16, Appendices O-T)

There were no microscopic or macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

11.G.1 Macroscopic

There were no early deaths among the animals submitted for histopathological evaluation.

Males

Incidental necropsy observations included: a small soft right testicle and small right epididymis in 1/10 Group 1 animals.

Females

Incidental necropsy observations included: spleen stricture in 1/10 Group 3 animals and a fluid filled uterus in 4/10 Group 1 and 1/10 Group 3 animals.

At the Day 29/30 time point, there were no macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. In the female rats, the presence of "fluid filled" uteri (which correlated with dilation), typically associated with normal proestrus stage of the estrous cycle, was decreased in rats treated with 512 and 1536 mg/kg/day Soy Leghemoglobin Preparation. Fluid filled uteri were noted in 4 out of 10 females at 0 mg/kg/day (Group 1 Animals 7013, 7017, 7018, and 7020), in 0 out of 10 females at 512 mg/kg/day, in 1 out of 10 females at 1024 mg/kg/day (Group 3 Animal 7053), and in 0 out of 10 females at 1536 mg/kg/day. Fluid filled uteri correlated with the proestrus stage of the estrus cycle, and higher individual uterine weights, and is a normal finding with this stage of the cycle. The decreased macroscopic incidence of fluid filled uteri in treated female rats correlated with lower incidences of proestrus, resulting in significantly decreased uterine weights in the 512 and 1536 mg/kg/day groups. Notably, the incidences of animals in metestrus in the treated groups were not dose-related.

The remaining macroscopic observations at the Day 29/30 time point were also of sporadic incidence and showed no trends/patterns to suggest a relationship to administration of Soy Leghemoglobin Preparation. These findings included testis and epididymis small and/or soft right which had a microscopic correlate of atrophy and aspermia, respectively, in control group Animal 7002; brain depressed area, which was an artifact confirmed microscopically, in Group 3 Animal 7047; and spleen stricture, with no microscopic correlate, in Group 3 Animal 7055.

11.G.2 Microscopic

At the Day 30 time point, there were no Soy Leghemoglobin Preparation-related effects.

There was a decrease in the incidence of dilated uterine lumens in the 536 and 1536 mg/kg/day rats compared to controls. The uteri were dilated in 4 out of 10 females at 0 mg/kg/day (Animals 7013, 7017, 7018, and 7020), which was consistent with proestrus/estrus. There were no females with dilated uterine lumens in the 512 and 1536 mg/kg/day rats and two out of 8 in the 1024 mg/kg/day group (Animals 7053 and 7059), which correlated with lower incidences of animals in the proestrus/estrus stage of the estrus cycle. Microscopically, 512 and 1536 mg/kg/day rats tended to be in the metestrus stage of the estrous cycle, which correlated with the lower weights and was an unusual distribution. However, the presence of both new and old corpora lutea in females from all groups indicates that these females were cycling normally and there were no treatment related effects on the estrus cycle.

All other microscopic findings at the Day 29/30 time point were unrelated to administration of Soy Leghemoglobin Preparation and can be observed in the age and strain of rats used in this study.

11.G.3 Organ Weights and Ratios

There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

Males

Mean absolute and relative organ weights for Groups 2-4 were comparable to control Group 1 values throughout the study.

Females

Mean absolute and relative organ weights for Groups 2-4 were generally comparable to control Group 1 values throughout the study with the exception of decreases in mean absolute and relative uterus weights in Groups 2-4 that were statistically significant ($p <$ 0.05-0.01) in Group 2 and Group 4 animals.

12. CONCLUSION

There were no mortalities, clinical observations, ophthalmology, body weight, body weight gain, food consumption, or food efficiency changes attributable to Soy Leghemoglobin Preparation administration.

There were no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or females rats. Changes in coagulation paramenters were limited to a non dose dependend increase in activated partial tromboplastin time observed in Group 3 and 4 males, that due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non adverse.

There were no microscopic or macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

Under the conditions of the study and based on the toxicological endpoints evaluated, the no-adverse-effect level (NOAEL) for administration of Soy Leghemoglobin Preparation in the diet was determined to be 1536 mg/kg/day, which corresponds to 750 mg/kg/day of the active ingredient Soy Leghemoglobin for Sprague Dawley rats.

13. REFERENCES

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TABLE 1A: CHEMICAL ANALYSIS RESULTS

Results for Neat Test Substance Stability Samples

Sampling Day	Measured Recovery (%)	% Change[1]	Overall Stability (%)
Day 0 (Initial)	94.96%	0.00%	100.00%
Day 14 (Middle)	95.29%	0.35%	100.35%
Day 21 (Final)	90.88%	-4.30%	95.70%

1 $\frac{\text{Final Sample} - \text{Initial Sample}}{\text{Initial Sample}} \times 100$

TABLE 1B: CHEMICAL ANALYSIS RESULTS

Results for Dietary Stability of Initial Samples

Day[1]	Group	Target Concentration Test Substance (ppm)	Measured Concentration Test Substance (ppm)	% of Target[2]
0	1 (BO)	0	ND	NA
	2 (M)	4373	4508	103.08%
	2 (F)	4711	4645	98.61%
	3 (M)	8746	7951	90.91%
	3 (F)	9422	9034	95.89%
	4(M)	13118	12265	93.50%
	4(F)	14133	12808	90.62%
4	1 (BO)	0	ND	NA
	2 (M)	4373	4207	96.20%
	2 (F)	4711	4471	94.90%
	3 (M)	8746	8238	94.19%
	3 (F)	9422	8918	94.65%
	4(M)	13118	12097	92.22%
	4(F)	14133	13191	93.33%
7	1 (BO)	0	ND	NA
	2 (M)	4373	4202	96.09%
	2 (F)	4711	4468	94.84%
	3 (M)	8746	8200	93.76%
	3 (F)	9422	8728	92.63%
	4(M)	13118	12423	94.70%
	4(F)	14133	13547	95.85%
10	1 (BO)	0	ND	NA
	2 (M)	4373	3968	90.74%
	2 (F)	4711	4693	99.63%
	3 (M)	8746	8453	96.65%
	3 (F)	9422	8836	93.78%
	4(M)	13118	12825	97.77%
	4(F)	14133	13762	97.38%

ND = Not Detected; NA = Not Applicable

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100

TABLE 1C: CHEMICAL ANALYSIS RESULTS

Results for Homogeneity of Dietary Preparations

Day[1]	Group	Sample Location	Target Concentration Test Substance (ppm)	Measured Concentration Test Substance (ppm)	% of Target[2]	Average % of Target	RSD (%)
0	1 (BO)	Middle	0	ND	NA	NA	NA
	2 (M)	Top	4373	4302	98.38%	95.87%	2.92%
		Middle		4061	92.86%		
		Bottom		4215	96.38%		
	2 (F)	Top	4711	4853	103.01%	98.01%	4.77%
		Middle		4583	97.28%		
		Bottom		4416	93.74%		
	3 (M)	Top	8746	8636	98.74%	95.40%	3.09%
		Middle		8145	93.13%		
		Bottom		8250	94.33%		
	3 (F)	Top	9422	9669	102.62%	97.71%	5.50%
		Middle		9284	98.53%		
		Bottom		8666	91.98%		
	4 (M)	Top	13118	12226	93.20%	97.85%	5.24%
		Middle		13558	103.35%		
		Bottom		12724	97.00%		
	4 (F)	Top	14133	14567	103.07%	98.64%	5.57%
		Middle		14183	100.35%		
		Bottom		13072	92.49%		

[1] Day relative to initial dietary preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100.

TABLE 1D: CHEMICAL ANALYSIS RESULTS

Results for Concentration Verification of Dietary Preparations

Day[1]	Group	Target Concentration Test Substance (ppm)	Measured Concentration Test Substance (ppm)	% of Target[2]
0[3]	1 (BO)	0	ND	NA
	2 (M)	4373	4061	92.86%
	2 (F)	4711	4583	97.28%
	3 (M)	8746	8145	93.13%
	3 (F)	9422	9284	98.53%
	4(M)	13118	13558	103.35%
	4(F)	14133	14183	100.35%
7	1 (BO)	0	ND	NA
	2 (M)	6093	6158	101.06%
	2 (F)	5824	5326	91.45%
	3 (M)	12318	12189	98.96%
	3 (F)	11664	11408	97.81%
	4(M)	18362	19409	105.70%
	4(F)	17567	17238	98.13%
21	1 (BO)	0	ND	NA
	2 (M)	7407	6906	93.24%
	2 (F)	5925	5498	92.80%
	3 (M)	14727	14292	97.05%
	3 (F)	12901	12612	97.76%
	4(M)	21943	20786	94.73%
	4(F)	19281	18829	97.65%

ND = Not Detected; NA = Not Applicable

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100.

[3] As part of the homogeneity analysis.

TABLE 2: SUMMARY OF CLINICAL OBSERVATIONS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Day numbers relative to Start Date

Sex: Male

	0 mg/kg/day	512 mg/kg/day	1024 mg/kg/day	1536 mg/kg/day
Staining				
Number of Observations	.	.	.	7
Number of Animals	.	.	.	7
Days from - to	.	.	.	13 13
Eschar				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	1
Days from - to	.	.	.	28 29

Day numbers relative to Start Date

Sex: Female

	0 mg/kg/day	512 mg/kg/day	1024 mg/kg/day	1536 mg/kg/day
Alopecia				
Number of Observations	.	10	.	.
Number of Animals	.	1	.	.
Days from - to	.	21 30	.	.

TABLE 3: SUMMARY OF DETAILED CLINICAL OBSERVATIONS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

TABLE 3: SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Males

Study Days 0, 7, 14, 21, and 28

Group	1	2	3	4
Dietary Concentration (mg/kg/day)	0	512	1024	1536
Number of Animals in Group	10	10	10	10
Observations During Removal From Cage And Handling	Score[1]			
Handling Reactivity	0	0	0	0
Vocalization	0	0	0	0
Palpebral Closure	0	0	0	0
Lacrimation	0	0	0	0
Eyes	0	0	0	0
Mucous Membranes	0	0	0	0
Salivation	0	0	0	0
Emaciation	0	0	0	0
Piloerection	0	0	0	0
Fur/Skin	0	0	0	0
Muscle Tone	0	0	0	0
Respiratory Pattern	0	0	0	0
Open Field Observations				
Activity/Arousal	0	0	0	0
Convulsions	0	0	0	0
Tremors	0	0	0	0
Posture	0	0	0	0
Gait	0	0	0	0
Locomotion	0	0	0	0
Vocalizations	0	0	0	0
Defecation	0	0	0	0
Urination	0	0	0	0
Unusual Behaviors	0	0	0	0
Pupillary Response				
Pupillary Reflex	0	0	0	0

[1] An entry of 0 indicates that all animals in the group appeared normal when evaluated for the specified observation, or that all animals did not exhibit the specific clinical sign. An entry greater than 0 indicates the number of animals in the group that exhibited the specific clinical sign. A number in the parenthesis (if present) represents the score given for the observed clinical sign.

TABLE 3 (cont.): SUMMARY OF DETAILED CLINICAL OBSERVATIONS

FEMALES

Study Days 0, 7, 14, 21, and 28

Group	1	2	3	4
Dietary Concentration (mg/kg/day)	**0**	**512**	**1024**	**1536**
Number of Animals in Group	**10**	**10**	**10**	**10**
Observations During Removal From Cage And Handling		**Score[1]**		
Handling Reactivity	0	0	0	0
Vocalization	0	0	0	0
Palpebral Closure	0	0	0	0
Lacrimation	0	0	0	0
Eyes	0	0	0	0
Mucous Membranes	0	0	0	0
Salivation	0	0	0	0
Emaciation	0	0	0	0
Piloerection	0	0	0	0
Fur/Skin	0	1(3)	0	0
Muscle Tone	0	0	0	0
Respiratory Pattern	0	0	0	0
Open Field Observations				
Activity/Arousal	0	0	0	0
Convulsions	0	0	0	0
Tremors	0	0	0	0
Posture	0	0	0	0
Gait	0	0	0	0
Locomotion	0	0	0	0
Vocalizations	0	0	0	0
Defecation	0	0	0	0
Urination	0	0	0	0
Unusual Behaviors	0	0	0	0
Pupillary Response				
Pupillary Reflex	0	0	0	0

[1] An entry of 0 indicates that all animals in the group appeared normal when evaluated for the specified observation, or that all animals did not exhibit the specific clinical sign. An entry greater than 0 indicates the number of animals in the group that exhibited the specific clinical sign. A number in the parenthesis (if present) represents the score given for the observed clinical sign.

TABLE 4: SUMMARY OF MEAN BODY WEIGHTS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Bodyweight (g)

Sex: Male Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0	Mean	236.4 1[1]	236.4	236.7	236.3
	SD	6.1	6.1	7.0	6.7
	N	10	10	10	10
7	Mean	287.7 1[1]	289.6	290.9	292.8
	SD	14.0	11.1	14.3	12.2
	N	10	10	10	10
14	Mean	332.3 1[1]	337.0	341.6	339.5
	SD	16.5	18.4	24.2	18.6
	N	10	10	10	10
21	Mean	373.2 1[1]	376.6	381.5	379.9
	SD	22.7	21.4	31.1	22.7
	N	10	10	10	10
28	Mean	394.7 1[1]	398.9	410.2	405.5
	SD	28.8	26.4	37.2	24.4
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]

Bodyweight (g)

Sex: Female Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0	Mean	174.1 I[1]	174.4	175.6	174.3
	SD	12.3	12.6	11.8	11.9
	N	10	10	10	10
7	Mean	198.3 I[1]	201.0	204.0	199.3
	SD	14.8	16.5	13.3	10.5
	N	10	10	10	10
14	Mean	218.8 I[1]	218.5	223.7	221.3
	SD	21.9	19.6	14.6	14.3
	N	10	10	10	10
21	Mean	239.2 I[1]	229.1	238.8	238.0
	SD	24.0	19.4	19.4	13.1
	N	10	10	10	10
28	Mean	249.8 I[1]	244.0	253.2	248.7
	SD	24.0	23.3	17.7	12.4
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]

TABLE 5: SUMMARY OF MEAN DAILY BODY WEIGHT GAIN[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Mean Daily Body Weight Gain (g/day)

Sex: Male Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 7	Mean	7.33 I[1]	7.60	7.74	8.07
	SD	1.35	0.94	1.40	1.16
	N	10	10	10	10
7 → 14	Mean	6.37 I[1]	6.77	7.24	6.67
	SD	0.77	1.30	1.49	1.13
	N	10	10	10	10
14 → 21	Mean	5.84 I[1]	5.66	6.13	5.77
	SD	1.15	0.75	1.12	0.86
	N	10	10	10	10
21 → 28	Mean	3.07 I[1]	3.19	3.67	3.66
	SD	1.06	0.91	1.10	0.47
	N	10	10	10	10
0 → 28	Mean	5.65 I[1]	5.80	6.20	6.04
	SD	0.84	0.83	1.14	0.70
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]

Mean Daily Body Weight Gain (g/day)

Sex: Female Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 7	Mean	3.46 I[1]	3.80	4.06	3.57
	SD	1.03	0.96	0.72	0.61
	N	10	10	10	10
7 → 14	Mean	2.93 R[2]	2.50	2.81	3.14
	SD	2.09	0.75	0.66	0.81
	N	10	10	10	10
14 → 21	Mean	2.91 I,A[3]	1.51 DD[5]	2.16	2.39
	SD	1.15	0.82	1.03	0.96
	N	10	10	10	10
21 → 28	Mean	1.51 L[4]	2.13	2.06	1.53
	SD	1.03	0.85	0.63	0.79
	N	10	10	10	10
0 → 28	Mean	2.70 I[1]	2.49	2.77	2.66
	SD	0.60	0.53	0.30	0.34
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [I,A - Automatic Transformation: Identity (No Transformation), (All Groups) Test: Analysis of Variance $p < 0.05$]
4 [L - Automatic Transformation: Log]
5 [DD - Test: Dunnett 2 Sided $p < 0.01$]

TABLE 6: SUMMARY OF MEAN DAILY FOOD CONSUMPTION[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Mean Daily Food Consumption (g/day)

Sex: Male Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 3	Mean	18.73 R[1]	18.73	18.80	19.03
	SD	3.35	1.98	2.68	2.99
	N	10	10	10	10
3 → 7	Mean	28.03 R[1]	28.60	28.23	28.63
	SD	1.08	0.52	2.08	1.07
	N	10	10	10	10
0 → 7	Mean	24.04 R[1]	24.37	24.19	24.51
	SD	1.67	0.65	0.94	1.56
	N	10	10	10	10
7 → 10	Mean	26.30 R[1]	27.10	27.80 dd[2]	27.90 d[3]
	SD	1.31	0.81	1.97	0.78
	N	10	10	10	10
10 → 14	Mean	26.55 R[1]	27.25	27.88	27.45
	SD	1.17	0.91	2.25	1.03
	N	10	10	10	10
7 → 14	Mean	26.44 R[1]	27.19	27.84 d[3]	27.64
	SD	1.16	0.84	2.12	0.84
	N	10	10	10	10
14 → 17	Mean	25.90 R[1]	25.47	26.33	26.17
	SD	0.89	1.83	2.71	0.82
	N	10	10	10	10
17 → 21	Mean	26.38 R[1]	26.50	27.10	26.93
	SD	0.97	0.77	2.31	0.86
	N	10	10	10	10
14 → 21	Mean	26.17 R[1]	26.06	26.77	26.60
	SD	0.93	1.19	2.42	0.67
	N	10	10	10	10
21 → 24	Mean	21.80 R[1]	22.07	22.27	22.47
	SD	0.77	1.03	1.61	0.66
	N	10	10	10	10
24 → 28	Mean	27.70 R[1]	28.75	29.13	29.18
	SD	1.04	1.21	1.92	1.28
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test   Transformation: Automatic

1 [R - Automatic Transformation: Rank]
2 [dd - Test: Dunn 2 Sided p < 0.01]
3 [d - Test: Dunn 2 Sided p < 0.05]

Mean Daily Food Consumption (g/day)

Sex: Male Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
21 → 28	Mean	25.17 R[1]	25.89	26.19	26.30
	SD	0.89	1.10	1.73	0.83
	N	10	10	10	10
0 → 28	Mean	25.46 R[1]	25.88	26.25	26.26
	SD	0.91	0.87	1.58	0.90
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test   Transformation: Automatic

1 [R - Automatic Transformation: Rank]

Mean Daily Food Consumption (g/day)

Sex: Female Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 3	Mean	13.43 R[1]	12.93	13.73	13.70
	SD	2.05	2.21	1.74	2.56
	N	10	10	10	10
3 → 7	Mean	21.18 R[1]	21.23	21.05	20.18
	SD	1.24	1.13	1.31	0.77
	N	10	10	10	10
0 → 7	Mean	17.86 R[1]	17.67	17.91	17.40
	SD	0.98	1.06	1.02	0.82
	N	10	10	10	10
7 → 10	Mean	19.33 R[1]	18.43	19.30	18.90
	SD	2.23	0.54	2.26	0.96
	N	10	10	10	10
10 → 14	Mean	19.55 I[2]	20.45	19.45	19.08
	SD	1.59	2.02	1.12	1.11
	N	10	10	10	10
7 → 14	Mean	19.46 R[1]	19.59	19.39	19.00
	SD	1.83	1.29	1.52	1.02
	N	10	10	10	10
14 → 17	Mean	19.27 I[2]	19.40	18.47	18.73
	SD	1.34	0.76	1.22	1.17
	N	10	10	10	10
17 → 21	Mean	19.88 L[3]	20.08	19.35	19.13
	SD	1.72	1.18	1.52	0.64
	N	10	10	10	10
14 → 21	Mean	19.61 R[1]	19.79	18.97	18.96
	SD	1.53	0.64	1.35	0.61
	N	10	10	10	10
21 → 24	Mean	15.90 I[2]	16.23	15.97	15.63
	SD	0.74	0.68	0.34	0.55
	N	10	10	10	10
24 → 28	Mean	20.70 R[1]	21.33	21.08	20.45
	SD	1.38	1.44	0.91	0.55
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test   Transformation: Automatic

1 [R - Automatic Transformation: Rank]
2 [I - Automatic Transformation: Identity (No Transformation)]
3 [L - Automatic Transformation: Log]

Mean Daily Food Consumption (g/day)

Sex: Female Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
21 → 28	Mean	18.64 R[1]	19.14	18.89	18.39
	SD	1.09	0.96	0.54	0.32
	N	10	10	10	10
0 → 28	Mean	18.89 I[2]	19.05	18.79	18.44
	SD	1.23	0.81	1.09	0.61
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

1 [R - Automatic Transformation: Rank]
2 [I - Automatic Transformation: Identity (No Transformation)]

TABLE 7: SUMMARY OF FOOD EFFICIENCY[1,2]

[1] Food efficiency = $\frac{\text{Mean Daily Body Weight Gain}}{\text{Mean Daily Food Consumption}}$

[2] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.

Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.

Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Food Efficiency

Sex: Male Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 7	Mean	0.304 I[1]	0.312	0.319	0.329
	SD	0.046	0.038	0.051	0.046
	N	10	10	10	10
7 → 14	Mean	0.241 I[1]	0.248	0.258	0.241
	SD	0.025	0.043	0.041	0.040
	N	10	10	10	10
14 → 21	Mean	0.223 L[2]	0.217	0.227	0.217
	SD	0.044	0.022	0.026	0.031
	N	10	10	10	10
21 → 28	Mean	0.121 I[1]	0.123	0.139	0.139
	SD	0.040	0.032	0.040	0.019
	N	10	10	10	10
0 → 28	Mean	0.222 I[1]	0.224	0.235	0.230
	SD	0.031	0.028	0.034	0.027
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test   Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [L - Automatic Transformation: Log]

Food Efficiency

Sex: Female Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 7	Mean	0.193 I[1]	0.215	0.226	0.206
	SD	0.055	0.052	0.037	0.038
	N	10	10	10	10
7 → 14	Mean	0.148 R[2]	0.128	0.146	0.165
	SD	0.093	0.037	0.033	0.040
	N	10	10	10	10
14 → 21	Mean	0.149I,A[3]	0.077 DD[5]	0.112	0.126
	SD	0.057	0.042	0.049	0.052
	N	10	10	10	10
21 → 28	Mean	0.080 L[4]	0.111	0.109	0.083
	SD	0.052	0.041	0.033	0.044
	N	10	10	10	10
0 → 28	Mean	0.142 I[1]	0.131	0.147	0.144
	SD	0.027	0.028	0.011	0.019
	N	10	10	10	10

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [I,A - Automatic Transformation: Identity (No Transformation), (All Groups) Test: Analysis of Variance $p < 0.05$]
4 [L - Automatic Transformation: Log]
5 [DD - Test: Dunnett 2 Sided $p < 0.01$]

TABLE 8: SUMMARY OF MEAN DAILY DIETARY INTAKE OF SOY LEGHEMOGLOBIN PREPARATION[1]

1 Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Dietary Intake Variable (mg/kg/day)

Sex: Male Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 7	Mean	0.0	485.4	966.5	1459.8
	SD	0.0	20.9	42.5	103.0
	N	10	10	10	10
7 → 14	Mean	0.0	540.5	1095.9	1631.5
	SD	0.0	24.5	53.5	78.9
	N	10	10	10	10
14 → 21	Mean	0.0	503.2	1007.2	1513.7
	SD	0.0	30.7	61.7	81.1
	N	10	10	10	10
21 → 28	Mean	0.0	495.9	973.0	1473.9
	SD	0.0	33.2	49.1	92.5
	N	10	10	10	10
0 → 28	Mean	0.0	478.9	954.7	1438.2
	SD	0.0	24.7	36.0	78.6
	N	10	10	10	10

Dietary Intake Variable (mg/kg/day)

Sex: Female Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
0 → 7	Mean	0.0	498.0	995.9	1481.1
	SD	0.0	43.5	29.2	115.0
	N	10	10	10	10
7 → 14	Mean	0.0	541.9	1064.6	1604.6
	SD	0.0	49.9	39.2	116.7
	N	10	10	10	10
14 → 21	Mean	0.0	518.8	1015.1	1537.2
	SD	0.0	53.9	34.3	92.3
	N	10	10	10	10
21 → 28	Mean	0.0	482.4	994.0	1460.2
	SD	0.0	41.9	56.0	79.0
	N	10	10	10	10
0 → 28	Mean	0.0	497.8	983.4	1470.4
	SD	0.0	42.8	29.0	88.2
	N	10	10	10	10

TABLE 9: SUMMARY OF HEMATOLOGY VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
RBC (x10^6/µL)	22	Mean	7.72	7.60	7.61	7.70
		SD	0.23	0.34	0.35	0.27
		N	10	10	10	10
		%Diff	.	-1.6	-1.5	-0.3
HGB (g/dL)	22	Mean	15.6	15.4	15.5	15.9
		SD	0.3	0.6	0.6	0.4
		N	10	10	10	10
		%Diff	.	-1.5	-1.0	1.4
HCT (%)	22	Mean	45.5	45.1	45.1	45.9
		SD	0.9	1.5	1.7	0.8
		N	10	10	10	10
		%Diff	.	-0.9	-0.8	1.0
MCV (fL)	22	Mean	58.9	59.3	59.3	59.7
		SD	1.0	2.3	1.5	1.9
		N	10	10	10	10
		%Diff	.	0.7	0.7	1.3
MCH (pg)	22	Mean	20.3	20.3	20.4	20.6
		SD	0.5	0.9	0.5	0.7
		N	10	10	10	10
		%Diff	.	0.2	0.6	1.6
MCHC (g/dL)	22	Mean	34.4	34.2	34.4	34.5
		SD	0.4	0.4	0.3	0.5
		N	10	10	10	10
		%Diff	.	-0.5	-0.1	0.4
RDW (%)	22	Mean	12.1	12.5	12.5	12.3
		SD	0.3	0.5	0.3	0.5
		N	10	10	10	10
		%Diff	.	3.0	3.3	1.6
PLT (x10^3/µL)	22	Mean	1160	1202	1171	1227
		SD	121	69	76	185
		N	10	10	10	10
		%Diff	.	3.6	1.0	5.8

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
WBC (x10^3/µL)	22	Mean	13.00	14.41	11.13	13.45
		SD	1.33	2.67	1.82	4.41
		N	10	10	10	10
		%Diff	.	10.8	-14.4	3.4
ANEU (x10^3/µL)	22	Mean	1.91	1.99	1.75	1.57
		SD	0.67	0.43	0.43	0.62
		N	10	10	10	10
		%Diff	.	4.1	-8.1	-17.8
ALYM (x10^3/µL)	22	Mean	10.49	11.79	8.86	11.29
		SD	1.17	2.48	1.70	4.15
		N	10	10	10	10
		%Diff	.	12.4	-15.5	7.7
AMON (x10^3/µL)	22	Mean	0.31	0.34	0.28	0.30
		SD	0.10	0.11	0.05	0.10
		N	10	10	10	10
		%Diff	.	10.2	-9.8	-1.5
AEOS (x10^3/µL)	22	Mean	0.12	0.13	0.11	0.11
		SD	0.04	0.08	0.04	0.05
		N	10	10	10	10
		%Diff	.	4.4	-7.2	-7.6
ABAS (x10^3/µL)	22	Mean	0.09	0.09	0.07	0.10
		SD	0.03	0.04	0.02	0.06
		N	10	10	10	10
		%Diff	.	-5.0	-27.0	6.2
ALUC (x10^3/µL)	22	Mean	0.08	0.08	0.06	0.08
		SD	0.03	0.03	0.02	0.04
		N	10	10	10	10
		%Diff	.	-8.1	-27.0	-2.4
ARET (x10^3/µL)	22	Mean	232.6	235.8	246.3	243.8
		SD	31.2	40.7	24.1	41.1
		N	10	10	10	10
		%Diff	.	1.4	5.9	4.8

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
RBC (x10^6/µL)	22	Mean	7.59	8.01 #[1]	7.86	7.63
		SD	0.24	0.38	0.24	0.30
		N	10	10	10	10
		%Diff	.	5.6	3.6	0.6
HGB (g/dL)	22	Mean	15.3	16.2 #[1]	15.7	15.5
		SD	0.5	0.5	0.4	0.6
		N	10	10	10	10
		%Diff	.	5.7	2.5	0.9
HCT (%)	22	Mean	43.6	45.9 #[1]	44.7	44.0
		SD	1.2	1.2	1.3	1.7
		N	10	10	10	10
		%Diff	.	5.2	2.4	0.9
MCV (fL)	22	Mean	57.5	57.4	56.8	57.7
		SD	1.1	2.2	1.2	2.2
		N	10	10	10	10
		%Diff	.	-0.2	-1.1	0.4
MCH (pg)	22	Mean	20.2	20.2	20.0	20.3
		SD	0.3	0.7	0.5	0.7
		N	10	10	10	10
		%Diff	.	0.1	-1.0	0.3
MCHC (g/dL)	22	Mean	35.2	35.3	35.2	35.2
		SD	0.7	0.3	0.4	0.5
		N	10	10	10	10
		%Diff	.	0.3	0.1	0.0
RDW (%)	22	Mean	11.3	11.3	11.2	11.5
		SD	0.4	0.5	0.3	0.5
		N	10	10	10	10
		%Diff	.	0.1	-0.4	1.7
PLT (x10^3/µL)	22	Mean	1190	1176	1230	1229
		SD	108	127	115	114
		N	10	10	10	10
		%Diff	.	-1.1	3.4	3.3

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
WBC (x10^3/µL)	22	Mean	10.08	11.87	11.59	10.19
		SD	1.70	1.75	3.35	3.72
		N	10	10	10	10
		%Diff	.	17.7	15.0	1.1
ANEU (x10^3/µL)	22	Mean	1.48	1.56	1.68	1.54
		SD	0.30	0.58	0.85	1.10
		N	10	10	10	10
		%Diff	.	5.3	13.9	4.0
ALYM (x10^3/µL)	22	Mean	8.15	9.74	9.29	8.21
		SD	1.58	1.43	2.71	2.88
		N	10	10	10	10
		%Diff	.	19.5	14.0	0.7
AMON (x10^3/µL)	22	Mean	0.25	0.29	0.33	0.22
		SD	0.15	0.06	0.15	0.14
		N	10	10	10	10
		%Diff	.	16.7	32.5	-11.1
AEOS (x10^3/µL)	22	Mean	0.11	0.13	0.15	0.12
		SD	0.03	0.04	0.05	0.06
		N	10	10	10	10
		%Diff	.	21.4	35.8	9.0
ABAS (x10^3/µL)	22	Mean	0.04	0.07 #1	0.06	0.05
		SD	0.01	0.03	0.03	0.04
		N	10	10	10	10
		%Diff	.	93.2	64.1	46.7
ALUC (x10^3/µL)	22	Mean	0.05	0.07	0.07	0.05
		SD	0.02	0.02	0.03	0.04
		N	10	10	10	10
		%Diff	.	29.1	26.2	2.9
ARET (x10^3/µL)	22	Mean	205.8	182.4	169.1 #1	184.2
		SD	33.9	32.9	30.9	33.7
		N	10	10	10	10
		%Diff	.	-11.3	-17.8	-10.5

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

TABLE 10: SUMMARY OF COAGULATION VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

Sex: Male Day(s) Relative to Start Date			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
PT (sec)	29	Mean	10.7	10.7	10.6	10.6
		SD	0.3	0.4	0.2	0.2
		N	10	10	10	10
APTT (sec)	29	Mean	20.2	23.8	24.9 @1	23.9 @1
		SD	2.4	5.3	6.9	4.8
		N	10	10	10	10

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [@ - Test: Dunnett Non-Parametric 2 Sided $p < 0.05$]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
PT (sec)	30	Mean	10.0	9.8	10.0	9.8
		SD	0.2	0.2	0.3	0.2
		N	10	10	10	10
APTT (sec)	30	Mean	21.9	20.0	20.8	19.4
		SD	2.5	3.1	5.0	1.9
		N	10	10	10	10

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

TABLE 11: SUMMARY OF CLINICAL CHEMISTRY VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

Sex: Male Day(s) Relative to Start Date			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
AST (U/L)	22	Mean	73	76	79	78
		SD	8	9	7	8
		N	5	9	6	8
		%Diff	.	4.0	7.5	6.9
ALT (U/L)	22	Mean	29	28	28	30
		SD	4	4	3	4
		N	10	10	10	10
		%Diff	.	-3.1	-2.4	2.4
SDH (U/L)	22	Mean	8.2	8.1	8.4	8.0
		SD	1.4	1.7	2.4	1.4
		N	5	9	6	8
		%Diff	.	-0.8	2.7	-1.9
ALKP (U/L)	22	Mean	183	216	216	205
		SD	24	29	44	42
		N	10	10	10	10
		%Diff	.	18.6	18.5	12.3
BILI (mg/dL)	22	Mean	0.17	0.17	0.18	0.18
		SD	0.02	0.02	0.02	0.02
		N	10	10	10	10
		%Diff	.	1.2	4.1	5.9
BUN (mg/dL)	22	Mean	10	11	10	11
		SD	1	1	1	2
		N	10	10	10	10
		%Diff	.	4.8	-3.8	1.0
CREA (mg/dL)	22	Mean	0.22	0.23	0.23	0.21
		SD	0.01	0.02	0.02	0.02
		N	10	10	10	10
		%Diff	.	3.6	4.1	-5.9
CHOL (mg/dL)	22	Mean	76	73	72	67
		SD	16	27	14	12
		N	10	10	10	10
		%Diff	.	-3.4	-5.4	-11.7

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
TRIG (mg/dL)	22	Mean	66	67	67	68
		SD	17	13	17	26
		N	10	10	10	10
		%Diff	.	1.8	0.9	2.4
GLUC (mg/dL)	22	Mean	95	100	102	98
		SD	12	9	13	8
		N	10	10	10	10
		%Diff	.	5.4	7.1	2.6
TP (g/dL)	22	Mean	6.0	6.1	6.2	6.0
		SD	0.2	0.2	0.2	0.2
		N	10	10	10	10
		%Diff	.	0.7	2.8	0.2
ALB (g/dL)	22	Mean	3.1	3.2	3.3 #1	3.2
		SD	0.1	0.1	0.1	0.1
		N	10	10	10	10
		%Diff	.	2.2	4.1	1.9
GLOB (g/dL)	22	Mean	2.9	2.8	2.9	2.8
		SD	0.1	0.2	0.1	0.2
		N	10	10	10	10
		%Diff	.	-1.0	1.4	-1.7
CALC (mg/dL)	22	Mean	10.4	10.4	10.4	10.5
		SD	0.2	0.2	0.2	0.2
		N	10	10	10	10
		%Diff	.	-0.1	0.1	0.8
IPHS (mg/dL)	22	Mean	8.6	8.7	8.8	8.6
		SD	0.4	0.4	0.9	0.4
		N	5	9	6	8
		%Diff	.	0.6	2.1	-0.3
NA (mmol/L)	22	Mean	140.5	142.1	141.1	141.7
		SD	4.2	0.6	0.7	0.8
		N	10	10	10	10
		%Diff	.	1.1	0.4	0.9

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
K (mmol/L)	22	Mean	5.03	5.19	5.55 #1	5.10
		SD	0.25	0.26	0.61	0.25
		N	10	10	10	10
		%Diff	.	3.1	10.4	1.4
CL (mmol/L)	22	Mean	100.8	102.0	101.6	101.7
		SD	2.4	1.0	0.8	1.2
		N	10	10	10	10
		%Diff	.	1.2	0.8	0.9

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
AST (U/L)	22	Mean	69	69	64	65
		SD	6	10	8	6
		N	9	9	10	10
		%Diff	.	-0.3	-7.4	-6.5
ALT (U/L)	22	Mean	25	26	25	27
		SD	4	5	6	5
		N	10	10	10	10
		%Diff	.	2.8	-0.4	5.2
SDH (U/L)	22	Mean	8.7	8.1	8.0	9.9
		SD	2.2	1.2	0.9	2.5
		N	9	9	10	10
		%Diff	.	-7.4	-9.0	12.9
ALKP (U/L)	22	Mean	137	107 #1	121	108 #1
		SD	16	19	29	25
		N	10	10	10	10
		%Diff	.	-22.4	-12.1	-21.3
BILI (mg/dL)	22	Mean	0.18	0.19	0.20	0.19
		SD	0.02	0.02	0.02	0.03
		N	10	10	10	10
		%Diff	.	8.4	10.6	7.8
BUN (mg/dL)	22	Mean	12	11	12	12
		SD	2	1	2	1
		N	10	10	10	10
		%Diff	.	-11.5	-0.8	0.0
CREA (mg/dL)	22	Mean	0.28	0.26	0.27	0.28
		SD	0.02	0.02	0.03	0.03
		N	10	10	10	10
		%Diff	.	-6.9	-2.9	1.1
CHOL (mg/dL)	22	Mean	85	95	98	94
		SD	11	19	19	22
		N	10	10	10	10
		%Diff	.	12.2	15.6	11.2

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Sex: Female Day(s) Relative to Start Date			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
TRIG (mg/dL)	22	Mean	37	38	46	35
		SD	6	9	15	8
		N	10	10	10	10
		%Diff	.	3.5	24.9	-4.3
GLUC (mg/dL)	22	Mean	118	103 #1	104 #1	110
		SD	15	10	10	14
		N	10	10	10	10
		%Diff	.	-13.3	-12.0	-6.7
TP (g/dL)	22	Mean	6.4	6.7	6.8	6.7
		SD	0.3	0.4	0.3	0.4
		N	10	10	10	10
		%Diff	.	5.1	5.6	3.7
ALB (g/dL)	22	Mean	3.5	3.7	3.7	3.6
		SD	0.2	0.2	0.2	0.3
		N	10	10	10	10
		%Diff	.	4.0	4.6	3.4
GLOB (g/dL)	22	Mean	2.9	3.1	3.1 #1	3.0
		SD	0.1	0.2	0.2	0.1
		N	10	10	10	10
		%Diff	.	6.6	6.9	4.1
CALC (mg/dL)	22	Mean	10.5	10.9 #1	11.0 #1	10.7
		SD	0.3	0.3	0.3	0.4
		N	10	10	10	10
		%Diff	.	3.8	5.1	1.8
IPHS (mg/dL)	22	Mean	7.1	7.8	7.6	7.1
		SD	0.5	0.6	0.4	0.8
		N	9	9	10	10
		%Diff	.	9.7	6.5	-0.6
NA (mmol/L)	22	Mean	140.3	140.6	140.3	140.2
		SD	1.1	0.6	0.7	1.1
		N	10	10	10	10
		%Diff	.	0.2	0.0	0.0

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [# - Test: Dunnett 2 Sided $p < 0.05$]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
K (mmol/L)	22	Mean	4.56	4.63	4.72	4.74
		SD	0.33	0.38	0.21	0.38
		N	10	10	10	10
		%Diff	.	1.5	3.5	4.0
CL (mmol/L)	22	Mean	102.6	101.3 #[1]	101.1 #[1]	102.1
		SD	1.2	1.4	1.0	1.1
		N	10	10	10	10
		%Diff	.	-1.3	-1.5	-0.5

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

TABLE 12: SUMMARY OF URINALYSIS VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
UVOL (mL)	22	Mean	11.7	11.5	12.3	14.3
		SD	8.2	9.8	7.3	7.7
		N	10	10	10	10
		%Diff	.	-1.8	4.8	22.0
pH	22	Mean	6.5	6.5	6.6	6.6
		SD	0.3	0.4	0.4	0.4
		N	10	9	10	10
		%Diff	.	0.0	0.8	1.5
SG	22	Mean	1.027	1.027	1.026	1.024
		SD	0.019	0.015	0.015	0.019
		N	10	9	10	10
		%Diff	.	0.0	-0.1	-0.3
URO (EU/dL)	22	Mean	0.3	0.2	0.3	0.2
		SD	0.3	0.0	0.3	0.0
		N	10	9	10	10
		%Diff	.	-28.6	0.0	-28.6
UMTP (mg/dL)	22	Mean	104	241	124	111
		SD	49	365	80	97
		N	10	10	10	10
		%Diff	.	132.5	19.5	7.4

General Footnote: [Statistical Test Anova and Dunnett's test Transformation :Automatic]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
UVOL (mL)	22	Mean	7.8	6.8	6.5	6.6
		SD	6.4	5.1	3.0	4.1
		N	10	10	10	10
		%Diff	.	-12.3	-15.9	-14.9
pH	22	Mean	6.4	6.2	6.6	6.5
		SD	0.4	0.4	0.6	0.6
		N	10	10	10	10
		%Diff	.	-3.9	3.1	0.8
SG	22	Mean	1.037	1.035	1.028	1.030
		SD	0.027	0.023	0.011	0.013
		N	10	10	10	10
		%Diff	.	-0.2	-0.8	-0.6
URO (EU/dL)	22	Mean	0.2	0.2	0.2	0.3
		SD	0.0	0.0	0.0	0.3
		N	10	10	10	10
		%Diff	.	0.0	0.0	40.0
UMTP (mg/dL)	22	Mean	43	41	34	44
		SD	34	25	12	30
		N	10	10	10	10
		%Diff	.	-3.7	-20.0	3.5

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

TABLE 13: SUMMARY OF GROSS NECROPSY OBSERVATIONS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Removal Reason: ALL	Male				Female			
	0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4	0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
spleen								
Submitted	10	10	10	10	10	10	10	10
stricture						.	1	
testes-combined								
Submitted	10	10	10	10				
right: small; soft	1	.	.			.	.	.
uterus								
Submitted	.	.	.		10	10	10	10
fluid filled					4		1	
epididymides-combined								
Submitted	10	10	10	10	.	.	.	.
right: small	1		.			.	.	

TABLE 14: SUMMARY OF MEAN TERMINAL BODY AND ORGAN WEIGHTS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Terminal BW (g)	-	Mean	367.5	372.5	384.0	379.3
		SD	25.3	23.8	33.4	21.4
		N	10	10	10	10
Adrenal Glands Wt (g)	-	Mean	0.0654 I[1]	0.0655	0.0593	0.0672
		SD	0.0068	0.0112	0.0116	0.0098
		N	10	10	10	10
Brain Wt (g)	-	Mean	2.141 I[1]	2.143	2.186	2.152
		SD	0.095	0.110	0.140	0.105
		N	10	10	10	10
Epididymides Wt (g)	-	Mean	1.032 I[1]	1.088	1.035	1.008
		SD	0.123	0.083	0.131	0.100
		N	10	10	10	10
Heart Wt (g)	-	Mean	1.195 I[1]	1.254	1.272	1.219
		SD	0.104	0.121	0.113	0.088
		N	10	10	10	10
Kidneys Wt (g)	-	Mean	2.641 I[1]	2.678	2.789	2.800
		SD	0.297	0.219	0.246	0.241
		N	10	10	10	10
Liver Wt (g)	-	Mean	11.218 I[1]	11.182	12.317	12.093
		SD	1.657	0.691	1.804	1.452
		N	10	10	10	10
Spleen Wt (g)	-	Mean	0.831 I[1]	0.813	0.769	0.809
		SD	0.125	0.107	0.053	0.105
		N	10	10	10	10
Testes Wt (g)	-	Mean	3.148 R[2]	3.381	3.266	3.272
		SD	0.531	0.292	0.251	0.246
		N	10	10	10	10
Thymus Wt (g)	-	Mean	0.5205 I[1]	0.5661	0.5466	0.5276
		SD	0.1595	0.1162	0.1185	0.1097
		N	10	10	10	10

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Terminal BW (g)	-	Mean	229.2	225.6	236.3	233.8
		SD	22.3	22.7	14.5	11.9
		N	10	10	10	10
Adrenal Glands Wt (g)	-	Mean	0.0717 I[1]	0.0713	0.0664	0.0737
		SD	0.0067	0.0089	0.0092	0.0093
		N	10	10	10	10
Brain Wt (g)	-	Mean	2.007 I[1]	1.976	2.046	2.021
		SD	0.093	0.099	0.077	0.049
		N	10	10	10	10
Heart Wt (g)	-	Mean	0.840 I[1]	0.830	0.850	0.848
		SD	0.092	0.057	0.034	0.065
		N	10	10	10	10
Kidneys Wt (g)	-	Mean	1.752 I[1]	1.820	1.769	1.815
		SD	0.164	0.177	0.140	0.101
		N	10	10	10	10
Liver Wt (g)	-	Mean	7.156 I[1]	7.636	7.338	7.763
		SD	0.720	1.037	0.512	0.548
		N	10	10	10	10
Ovaries with Oviducts Wt (g)	-	Mean	0.1309 I[1]	0.1272	0.1231	0.1364
		SD	0.0173	0.0172	0.0143	0.0150
		N	10	10	10	10
Spleen Wt (g)	-	Mean	0.498 I[1]	0.518	0.507	0.513
		SD	0.089	0.119	0.068	0.060
		N	10	10	10	10
Thymus Wt (g)	-	Mean	0.4343 I[1]	0.4654	0.4762	0.5218
		SD	0.0998	0.0741	0.0967	0.1127
		N	10	10	10	10
Uterus Wt (g)	-	Mean	0.727 R[2]	0.457 dd[3]	0.615	0.490 d[4]
		SD	0.247	0.061	0.276	0.057
		N	10	10	10	10

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [dd - Test: Dunn 2 Sided p < 0.01]
4 [d - Test: Dunn 2 Sided p < 0.05]

TABLE 15: SUMMARY OF MEAN ORGAN-TO-BODY WEIGHT RATIOS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.

Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.

Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Adrenal /TBW (Ratio)	-	Mean	0.1781 I[1]	0.1766	0.1540	0.1773
		SD	0.0165	0.0328	0.0253	0.0264
		N	10	10	10	10
Brain /TBW (Ratio)	-	Mean	5.846 I[1]	5.766	5.722	5.682
		SD	0.411	0.355	0.497	0.294
		N	10	10	10	10
Epididymides /TBW (Ratio)	-	Mean	2.8075 I[1]	2.9351	2.7030	2.6712
		SD	0.2682	0.3125	0.3143	0.3544
		N	10	10	10	10
Heart /TBW (Ratio)	-	Mean	3.251 I[1]	3.362	3.315	3.214
		SD	0.151	0.151	0.128	0.149
		N	10	10	10	10
Kidneys /TBW (Ratio)	-	Mean	7.184 I[1]	7.199	7.274	7.387
		SD	0.610	0.541	0.421	0.560
		N	10	10	10	10
Liver /TBW (Ratio)	-	Mean	30.549 R[2]	30.052	31.962	31.893
		SD	4.348	1.405	2.654	3.559
		N	10	10	10	10
Spleen /TBW (Ratio)	-	Mean	2.256 I[1]	2.199	2.012	2.139
		SD	0.255	0.391	0.184	0.312
		N	10	10	10	10
Testes /TBW (Ratio)	-	Mean	8.549 I[1]	9.108	8.564	8.657
		SD	1.201	0.971	0.970	0.885
		N	10	10	10	10
Thymus /TBW (Ratio)	-	Mean	1.4134 I[1]	1.5209	1.4171	1.3939
		SD	0.4037	0.3105	0.2319	0.2919
		N	10	10	10	10

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Adrenal /TBW (Ratio)	-	Mean	0.3139 I[1]	0.3168	0.2812	0.3157
		SD	0.0265	0.0336	0.0372	0.0399
		N	10	10	10	10
Brain /TBW (Ratio)	-	Mean	8.801 I[1]	8.828	8.692	8.664
		SD	0.545	0.852	0.686	0.492
		N	10	10	10	10
Heart /TBW (Ratio)	-	Mean	3.665 I[1]	3.692	3.605	3.625
		SD	0.189	0.171	0.178	0.163
		N	10	10	10	10
Kidneys /TBW (Ratio)	-	Mean	7.657 I[1]	8.094	7.505	7.783
		SD	0.412	0.639	0.657	0.602
		N	10	10	10	10
Liver /TBW (Ratio)	-	Mean	31.278 I[1]	33.819	31.158	33.269
		SD	2.212	2.693	2.883	2.772
		N	10	10	10	10
Ovaries with oviducts/TBW (Ratio)	-	Mean	0.5727 I[1]	0.5635	0.5222	0.5835
		SD	0.0669	0.0474	0.0643	0.0581
		N	10	10	10	10
Spleen /TBW (Ratio)	-	Mean	2.171 I[1]	2.284	2.149	2.191
		SD	0.300	0.384	0.291	0.206
		N	10	10	10	10
Thymus /TBW (Ratio)	-	Mean	1.8863 I[1]	2.0742	2.0184	2.2362
		SD	0.3463	0.3287	0.4057	0.4918
		N	10	10	10	10
Uterus /TBW (Ratio)	-	Mean	3.159 [2]	2.060 DD	2.579	2.103 DD
		SD	0.949	0.452	1.063	0.277
		N	10	10	10	10

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [L,AA - Automatic Transformation: Log, (All Groups) Test: Analysis of Variance $p < 0.01$]
3 [DD - Test: Dunnett 2 Sided $p < 0.01$]

TABLE 16: SUMMARY OF MEAN ORGAN-TO-BRAIN WEIGHT RATIOS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Adrenal /BrW (Ratio)	-	Mean	0.0306 I[1]	0.0307	0.0270	0.0312
		SD	0.0031	0.0056	0.0043	0.0039
		N	10	10	10	10
Epididymides /BrW (Ratio)	-	Mean	0.4813 I[1]	0.5095	0.4738	0.4700
		SD	0.0465	0.0535	0.0521	0.0573
		N	10	10	10	10
Heart /BrW (Ratio)	-	Mean	0.558 R[2]	0.585	0.583	0.566
		SD	0.038	0.048	0.052	0.027
		N	10	10	10	10
Kidneys /BrW (Ratio)	-	Mean	1.232 I[1]	1.251	1.278	1.300
		SD	0.114	0.100	0.114	0.078
		N	10	10	10	10
Liver /BrW (Ratio)	-	Mean	5.238 I[1]	5.228	5.633	5.614
		SD	0.727	0.374	0.740	0.579
		N	10	10	10	10
Spleen /BrW (Ratio)	-	Mean	0.388 I[1]	0.380	0.353	0.376
		SD	0.057	0.055	0.039	0.044
		N	10	10	10	10
Testes /BrW (Ratio)	-	Mean	1.469 I[1]	1.581	1.498	1.523
		SD	0.235	0.155	0.123	0.125
		N	10	10	10	10
Thymus /BrW (Ratio)	-	Mean	0.2436 I[1]	0.2630	0.2502	0.2450
		SD	0.0739	0.0472	0.0514	0.0476
		N	10	10	10	10

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Adrenal /BrW (Ratio)	-	Mean	0.0357 I[1]	0.0361	0.0325	0.0365
		SD	0.0024	0.0043	0.0047	0.0050
		N	10	10	10	10
Heart /BrW (Ratio)	-	Mean	0.418 I[1]	0.420	0.416	0.420
		SD	0.031	0.028	0.026	0.036
		N	10	10	10	10
Kidneys /BrW (Ratio)	-	Mean	0.872 I[1]	0.920	0.866	0.898
		SD	0.056	0.062	0.080	0.049
		N	10	10	10	10
Liver /BrW (Ratio)	-	Mean	3.566 I[1]	3.862	3.592	3.842
		SD	0.325	0.476	0.310	0.267
		N	10	10	10	10
Ovaries with oviducts/BrW (Ratio)	-	Mean	0.0652 I[1]	0.0644	0.0603	0.0676
		SD	0.0075	0.0086	0.0079	0.0078
		N	10	10	10	10
Spleen /BrW (Ratio)	-	Mean	0.248 I[1]	0.261	0.248	0.254
		SD	0.039	0.054	0.035	0.031
		N	10	10	10	10
Thymus /BrW (Ratio)	-	Mean	0.2158 I[1]	0.2366	0.2332	0.2583
		SD	0.0459	0.0434	0.0489	0.0561
		N	10	10	10	10
Uterus /BrW (Ratio)	-	Mean	0.361 R[2]	0.232 dd[3]	0.301	0.242 d[4]
		SD	0.118	0.033	0.136	0.028
		N	10	10	10	10

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [dd - Test: Dunn 2 Sided p < 0.01]
4 [d - Test: Dunn 2 Sided p < 0.05]

APPENDIX A: PROTOCOL AND PROTOCOL AMENDMENTS

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

SOY LEGHEMOGLOBIN PREPARATION: A 28-DAY DIETARY STUDY IN RATS

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

PSL PROTOCOL NO.

P703.01 IMP

PERFORMING LABORATORY

Product Safety Labs
2394 US Highway 130
Dayton, New Jersey 08810

PSL STUDY NUMBER

43166

STUDY DIRECTOR

Mithila Shitut, BVSc & AH, MS

SPONSOR

Impossible Foods, Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

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Product Safety Labs

1. **TITLE OF STUDY: SOY LEGHEMOGLOBIN PREPARATION: A 28-DAY DIETARY STUDY IN RATS**

2. **OBJECTIVE**

   The objective of this study is to evaluate the potential subchronic toxicity of Soy Leghemoglobin Preparation in male and female rats continuously exposed to the test substance in the diet for at least 28 days. A no-observed-adverse-effect-level (NOAEL) is sought for each sex.

3. **STUDY DIRECTOR**

   Mithila Shitut
   Study Director
   Tel: 732-438-5100 x1558
   Email: MithilaShitut@ProductSafetyLabs.com

4. **NAME AND ADDRESS OF THE TESTING FACILITY**

   Product Safety Labs (PSL)
   2394 US Highway 130
   Dayton, NJ 08810
   Tel: 732 438 5100

5. **SPONSOR**

   Impossible Foods, Inc.
   525 Chesapeake Dr.
   Redwood City, CA 94063

6. **SPONSOR REPRESENTATIVE**

   Rachel Fraser
   Impossible Foods, Inc.
   525 Chesapeake Dr.
   Redwood City, CA 94063
   Email: rachel.fraser@impossiblefoods.com

7. **DATES**

   Proposed In-Life Start Date: 9/28/16

   Proposed Experimental Termination Date: 10/28/16

8. **TEST SUBSTANCE**

   8.A Source

   The test substance will be provided by the Sponsor.

8.B Identification

The test substance will be identified using the following information provided by the Sponsor and Product Safety Labs (PSL) identification number.

Test Substance: Soy Leghemoglobin Preparation
PSL ID: 160720-5R
Lot #: PP-PGM2-16-088-301
Physical Description: Red/brown powder
Composition: Soy Leghemoglobin 48.82%
Storage Conditions: Frozen
Expiration Date: Not Applicable

Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

8.C Analysis

The test substance, as received, is expected to be stable for the duration of the study. Stability of the test substance in the dietary matrix and that of the concentration of the test substance in the test diets will be determined as part of this study.

8.D Hazards

Appropriate routine safety precautions will be exercised in the handling of the test substance unless otherwise indicated by the Sponsor.

9. GENERAL TEST SYSTEM PARAMETERS

9.A Animal Requirements

9.A.1 Number of Animals: 80

9.A.2 Number of Groups: 4 (3 dietary levels per sex + 1 control group per sex)

9.A.3 Number of Animals per Group: 20 (10 male, 10 female)

9.A.4 Sex: Male and female; females will be nulliparous and non-pregnant.

9.A.5 Species/Strain: CRL Sprague-Dawley CD® IGS rats

9.A.6 Age/Weight: Seven to eight weeks at initiation; the weight variation will not exceed ± 20% of the mean weight for each sex.

9.A.7 Supplier: Charles River Laboratories, Inc. Rats will be shipped in filtered cartons by airfreight and/or truck.

9.B Test System Justification

The Sprague-Dawley® rat is the system of choice because, historically, it has been a preferred and commonly used species for dietary toxicity tests. The current state of scientific knowledge does not provide acceptable alternatives to the use of live animals to accomplish the objective of this study.

9.C Husbandry

9.C.1 Housing

The animals will be group housed in suspended stainless steel cages, which conform to the size recommendations in the latest *Guide for the Care and Use of Laboratory Animals*[1]. Litter paper placed beneath the cage will be changed at least three times/week. The animal room will have a 12-hour light/dark cycle and will be kept clean and vermin free. Environmental controls are set to maintain temperature and relative humidity ranges of 21 ± 2°C and 30-70%, respectively. Observed ranges will be documented in the raw data.

9.C.2 Acclimation

The animals will be conditioned to the housing facilities for at least five days prior to testing. Body weights and clinical observations will be recorded at least two times prior to study start.

9.C.3 Feed

2016 Certified Envigo Teklad Global Rodent Diet® will be stored in a dedicated temperature and humidity monitored feed storage site and will be available *ad libitum* during acclimation. Test diets will be prepared as described in Section 11.B using 2016 certified Envigo Teklad Global Rodent Diet® and will be available *ad libitum* during the study.

9.C.4 Water

Filtered tap water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. Water analysis is conducted by Precision Analytical Services, Inc., Toms River, NJ and South Brunswick Municipal Water Supply, South Brunswick, NJ.

9.C.5 Contaminants

There are no known contaminants reasonably expected to be found in the food or water that would interfere with the results of this study. Routine analysis consisting of each lot of feed used in this study will be received from Envigo Teklad, Madison, WI. Water analysis is conducted periodically and the records are kept on file at Product Safety Labs. The date(s) of the most recent analyses will be reported in the final report.

9.C.6 Viral Screen

Serum samples from naive rats housed in the same room as test animals, as part of PSL's sentinel health monitoring program, will be evaluated for the absence of viruses near the end of the in-life portion of the study (PSL SOP #755).

[1] National Research Council. (2011). *Guide for the Care and Use of Laboratory Animals (8th ed.)*. Washington, DC: The National Academies Press.

9.D Identification

9.D.1 Cage

Each cage will be identified by a cage card indicating at least the study number, dose level, group assignment, individual animal identification and sex of the animals.

9.D.2 Animal

Each animal will be given a sequential number in addition to being uniquely identified with a Monel® self-piercing stainless steel ear tag.

10. EXPERIMENTAL DESIGN

10.A Route of Administration

The test substance will be administered in the diet.

10.B Justification of Route of Administration

The dietary route of administration will be used because it is recommended in the referenced guidelines (Section 14.C.), and because human exposure may occur via this route.

10.C Control of Bias

Animals will be randomly assigned to test groups according to PSL SOP # 714.

10.D Dose Levels

Ten male and ten female test animals will be randomly assigned to each of the following test groups:

Group	No. Animals/ Group M/F	Dietary Dose Level/ Target Exposure of Active Ingredient (mg/kg/day)	Dietary Dose Level/ Target Exposure of Test Substance[a] (mg/kg/day)
1	10/10	0	0
2	10/10	250	512
3	10/10	500	1024
4	10/10	750	1536

[a]Based on 48.82% active ingredient (AI, Soy Leghemoglobin) of Soy Leghemoglobin Preparationlot # PP-PGM2-16-088-301

10.E Justification of Dose Level Selection

The Sponsor, in consultation with the Study Director, and based on a 14-day palatability/toxicity study (43167[1]) selected target dietary dose levels of 512, 1024 and 1536 mg/kg/day that correspond to target dose levels of 250, 500 and 750 mg/kg/day of the active ingredient, Soy leghemoglobin. To maintain target dietary dose levels throughout the study, concentrations in the test diets will be calculated based on the most recent group body weight and food consumption data. Alternatively, historical control values, relevant to the age and weight of the rats at

[1] Product Safety Labs (2016). Soy Leghemoglobin Preparation, Purified Soy Leghemoglobin Preparation and Bovine Erythrocytes: A 14-day dietary toxicity/palatability study in rats (In Draft).

corresponding intervals will be used. Diets for males and females at each dietary dose level will be made separately each week. A NOAEL is expected to be achieved for this study.

11. GENERAL PROCEDURES

11.A Selection of Animals

Eighty (80) healthy rats (forty males; forty females) will be used on test. Animals will be selected for this study on the basis of adequate body weight gain, absence of clinical signs of disease or injury, and a body weight within ±20% of the mean within a sex. Selected rats will be distributed by randomization according to stratification by body weight so that there will be no statistically significant difference among group body weight means within a sex.

11.B Diet Preparation and Sampling

11.B.1 Diet Preparation (PSL SOP #605)

The test substance will be processed as needed to decrease particle size using a grinder and then added to 2016 Envigo Teklad Global Rodent Diet® and thoroughly mixed in a high-speed mixer. Control diet will be mixed under the same conditions as the diets prepared with the test substance. All diets will be kept frozen following preparation, unless presented to the test animals on the same day as diet preparation. All diets will be prepared approximately weekly.

11.B.2 Diet Presentation

The control and test diets will be presented to their respective groups on Day 0 of the study. The diets will be replaced concurrently with food consumption measurements on Days 3, 7, 10, 14, 17, 21 and 24. Additional diet may be provided as needed throughout the study to insure *ad libitum* feeding. Animals will be exposed to the test diets for at least 28 days.

11.B.3 Sampling (PSL SOP #607)

The neat test substance and selected prepared diets (at each concentration), will be sampled in duplicate.

11.B.4 Stability of Test Substance

At the initial, middle, and final diet preparation, a sample of the test substance (neat) will be retained for stability. Analytical results of the initial and final stability samples will be used to establish the stability of the test substance under normal laboratory conditions for the duration of the study.

11.B.5 Stability in Dietary Matrix

During the first week of the study, samples to verify the stability of the test and control substance in the dietary matrix will be prepared. Samples will be prepared in standard feed jars with followers and retaining rings and will be stored at ambient temperature in the animal room. Samples from each dietary concentration will be collected at the first presentation of the diet and after 4, 7, and 10 days and frozen until analyzed.

11.B.6 Homogeneity

Samples to evaluate homogeneity of the test and control substance distribution will be collected from the initial diet preparation. Samples will be taken from approximately the top, middle and bottom of the diet mixer. Basal diet control samples will be collected from the middle of the mixer only. Chemical analysis will verify the diets as homogeneous and of accurate concentration throughout the study.

11.B.7 Concentration Verification

Samples will be collected from representative animal diets of the initial (as part of the homogeneity assessment), middle and final diet preparations during which time samples will be retained and stored frozen. Samples will be analyzed to verify the concentration of the test diets.

11.B.8 Sample Preservation

Upon sampling, diet preparations and neat test substance will be stored frozen. Samples will be considered stable from the point at which they are frozen.

11.B.9 Sample Analysis

A single duplicate of the frozen diet samples described above will be sent to Impossible Foods for analysis of diet preparation and neat test substance samples. A signed, analytical report will be provided to the Study Director. This report will include the methodology, pertinent measurements, study results, and tabulated results. Upon completion of the report, all raw data will be transferred to the Study Director to be incorporated into the main study report. Any remaining sample material will be retained at Product Safety Labs until issuance of the final report.

11.C Analytical Chemistry

11.C.1 Sample Storage

Upon receipt, all samples will be stored and maintained frozen (approximately -20°C) prior to analysis.

11.C.2 Method Validation

Prior to sample analysis, the suitability of the methods will be demonstrated. Method validation will include, but it not limited to determination of linearity, precision, and accuracy.

11.C.3 Reference Substance

Aliquots of the neat test substance will serve as the reference standard.

11.C.4 Chemical Analysis

Analytical test methodology will be validated by Impossible Foods personnel. Samples will be analyzed in replicate. A detailed description of the analytical test method(s) will be documented. Any remaining sample material will be retained until the issuance of the final report.

11.C.5 Data Reporting

Data will be captured on standard raw data sheets and as instrument output, as necessary, and summarized in tabular form.

11.C.6 Analytical Report and Records to be Maintained

A signed, analytical report will be provided to the Study Director. This report will include the methodology, pertinent measurements, study results, and tabulated results. Upon completion of the report, all raw data will be transferred to the Study Director. The analytical report will be incorporated into the main study report.

11.D Ophthalmologic Evaluations

During the acclimation period, the eyes of all rats being considered for study will be examined by focal illumination, indirect ophthalmoscopy and, when indicated, slit-lamp microscopy. Mydriatic eye drops will be administered prior to ophthalmoscopy and the eyes will be examined in subdued light. Subdued light will be maintained in the animal room according to PSL SOP #737. These procedures will be repeated on all surviving test animals prior to test termination.

11.E Clinical Observations

All animals will be observed at least twice daily for viability. Cage-side observations of all animals will be performed daily during the study. All findings will be recorded.

On Day 0, prior to the first treatment with the test substance, and approximately weekly thereafter, a detailed observation will be conducted (PSL SOP #726) while handling the animal, generally on days that the animals are weighed and food consumption measurements are taken. Potential signs noted should include, but not be limited to: changes in skin, fur, eyes, and mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Likewise, changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes (e.g., excessive grooming, repetitive circling), or bizarre behavior (e.g., self-mutilation, walking backwards) should also be recorded. The date and clock time of all observations and/or mortality checks will be recorded.

The Study Director will be promptly notified of severe/remarkable clinical observations and will be advised when an animal is found in a moribund condition and may authorize euthanasia and necropsy as necessary to avoid the loss of quality data. All such authorizations will be recorded in the raw data.

11.F Body Weight and Body Weight Gain

Individual body weights will be recorded at least two times during acclimation. Test animals will be weighed on Day 0 (prior to study start) and approximately weekly thereafter (intervals of 7 days ± 1). Decedents need not be weighed. Body weight gain will be calculated for selected intervals and for the study overall.

11.G Food Consumption, Food Efficiency, and Dietary Intake of Soy Leghemoglobin Preparation

Individual food consumption will be measured and recorded on Days 3, 7, 10, 14, 17, 21, 24 and at the end of the study. Food efficiency and dietary intake of the test substance (mg/kg/day) will also be calculated and reported.

11.H Clinical Pathology

Clinical pathology will be performed on all surviving animals for blood chemistry and hematology of the terminal sacrifice animals once toward the end of the dosing phase of the study. The animals will be fasted overnight prior to blood collection. Blood samples for hematology (except coagulation samples) and clinical chemistry will be collected via sublingual bleeding under isoflurane anesthesia during approximately Week 4 of the test period. Approximately 500 µL of blood will be collected in a pre-calibrated tube containing K_2EDTA for hematology assessments. The whole blood samples will be stored under refrigeration and shipped on cold packs. Approximately 1000 µL of blood will be collected into a tube containing no preservative for clinical chemistry assessments. These samples will be centrifuged in a refrigerated centrifuge and the serum will be transferred to a labeled tube. Serum samples will be stored in a -80°C freezer and shipped frozen on dry ice. All samples will be shipped to DuPont Haskell Global Centers for Health and Environmental Sciences.

The day before collection of samples for the clinical pathology evaluation, the animals will be placed in metabolism cages. Animals will be fasted after 3 pm (at least 15 hours prior to) and urine will be collected from each animal. Urine samples will be stored under refrigeration and shipped on cold packs or wet ice to DuPont Haskell Global Centers for Health and Environmental Sciences.

Blood samples used to determine the prothrombin time and activated partial thromboplastin time (coagulation) will be collected via the inferior vena cava under isoflurane anesthesia at terminal sacrifice. Approximately 1.8 mL of blood will be collected in a pre-calibrated tube containing 3.2% sodium citrate. These samples will be centrifuged in a refrigerated centrifuge and the plasma will be transferred to labeled tubes. Plasma samples will be stored in a -80°C freezer and shipped frozen in dry ice to DuPont Haskell Global Centers for Health and Environmental Sciences. In addition, a second blood sample will be retained during the exsanguination procedure for future possible evaluation if treatment related effects are identified. Details of this evaluation will be added by amendment.

All blood samples will be evaluated for quality by visual examination.

11.H.1 Hematology: Will include:

erythrocyte count (RBC)	hemoglobin concentration (HGB)
hematocrit (HCT)	mean corpuscular volume (MCV)
mean corpuscular hemoglobin (MCH)	red cell distribution width (RDW)
absolute reticulocyte count (ARET)	platelet count (PLT)

total white blood cell (WBC) and differential leukocyte count
Mean corpuscular hemoglobin concentration (MCHC) will be calculated.

In addition, separate, blood smears, stained with New Methylene Blue or Wright-Giemsa stain, will be prepared from each animal undergoing hematological evaluation and will be examined, if required, to substantiate or clarify the results of hematology findings.

11.H.2 Coagulation: Will include:

prothrombin time (PT)
activated partial thromboplastin time (APTT)

11.H.3 Clinical chemistry: Will include:

serum aspartate amino transferase (AST)	serum alanine aminotransferase (ALT)
sorbitol dehydrogenase (SDH)	alkaline phosphatase (ALKP)
total bilirubin (BILI)	urea nitrogen (BUN)
blood creatinine (CREA)	total cholesterol (CHOL)
triglycerides (TRIG)	fasting glucose (GLUC)
total serum protein (TP)	albumin (ALB)
globulin (GLOB)	calcium (CALC)
inorganic phosphorus (IPHS)	sodium (NA)
potassium (K)	chloride (CL)

11.H.4 Urinalysis: Will include:

quality (QUAL)	pH	ketone (KET)
color (COL)	glucose (UGLC)	bilirubin (UBIL)
clarity (CLAR)	specific gravity (SG)	blood (BLD)
volume (UVOL)	protein (UMTP)	urobilinogen (URO)

microscopic urine sediment examination

Any remaining serum samples will be maintained frozen at approximately -80°C and discarded upon approval of the Sponsor at finalization.

11.I Terminal Sacrifice and Histopathology

11.I.1 Scheduled Sacrifice

At terminal sacrifice, all survivors will be euthanized by exsanguination from the abdominal aorta under isoflurane anesthesia. All animals in the study (including decedents) will be subjected to a gross necropsy, which will include examination of the external surface of the body, all orifices, musculoskeletal system, and the cranial, thoracic, abdominal, and pelvic cavities, with their associated organs and tissues. All gross lesions will be recorded. The following tissues (of all animals sacrificed by design) will be weighed wet as soon as possible after dissection to avoid drying:

adrenals (combined)	kidneys (combined)	spleen
brain	liver	thymus
epididymides (combined)	ovaries with oviducts (combined)	uterus
heart	testes (combined)	

The following organs and tissues from all animals will be preserved in 10% neutral buffered formalin for possible future histopathological examination:

accessory genital organs (prostate and seminal vesicles)	ileum with Peyer's patches	rectum
adrenals	jejunum	salivary glands (sublingual submandibular, and parotid)
all gross lesions	kidneys	skeletal muscle
aorta	larynx	skin
bone (femur)	liver	spinal cord - 3 levels: cervical, mid- thoracic, and lumbar
bone marrow (from femur & sternum)	lungs	spleen
brain – 3 sections including medulla/pons, cerebellar, and cerebral cortex	lymph node mandibular	sternum
cecum	lymph node mesenteric	stomach
cervix	mammary gland	thymus
colon	nasal turbinates	thyroid
duodenum	nose	trachea
esophagus	ovaries	urinary bladder
Harderian gland	oviducts	uterus
heart	pancreas	vagina
	parathyroid	
	peripheral nerve (sciatic)	
	pharynx	
	pituitary gland	

The following organs and tissues from all animals will be preserved in modified Davidson's fixative and then stored in ethanol for possible future histopathological examination:

eyes	optic nerve
epididymides	testes

Additional tissues will be preserved if indicated by signs of toxicity or target organ involvement.

11.1.2 Unscheduled Sacrifice

Any rat that dies or is sacrificed because of a moribund condition will be examined for the cause of death or moribund condition on the day the observation is made. Rats will be evaluated for gross lesions. Organs and tissues will be excised, weighed (except for animals found dead), and preserved as described for those animals sacrificed by design.

11.1.3 Histopathology

Histological examination will be performed on the preserved organs and tissues of the animals from both the control and high dose groups (Groups 1 and 4, respectively) as well as from any animal that dies during the course of the study. In addition, gross lesions of potential toxicological significance noted in any test groups at the time of terminal sacrifice will also be examined. These examinations may be extended to other tissues and organs from the low and intermediate groups at the request of Pathologist in consultation with the Study Director and Sponsor to further investigate changes observed in the high dose group. The fixed tissues will be trimmed, processed, embedded in paraffin, sectioned with a microtome, placed on glass microscope slides, stained with hematoxylin and eosin (HE) and examined by light microscopy. Additional special stains can be added based on HE evaluation at the discretion of the study pathologist in consultation with the study director and sponsor. Slide preparation and histological assessment, by a board-certified veterinary pathologist, will be performed at Histo-Scientific Research Laboratories (HSRL).

12. STATISTICAL ANALYSIS

Product Safety Labs will perform statistical analysis of all data collected during the in-life phase of the study as well as organ weight data, if applicable. The use of the word "significant" or "significantly" indicates a statistically significant difference between the control and the experimental groups. Significance will be judged at a probability value of $p < 0.05$. Male and female rats will be evaluated separately.

12.A Statistical Methods (In-Life and Organ Weight Data):

Mean and standard deviations will be calculated for all quantitative data. If warranted by sufficient group sizes, data within groups will be evaluated for homogeneity of variance[1] and normality. Where homogeneous variance and normal distribution is observed, treatment and control groups will be compared using a one-way analysis of variance (ANOVA). When one-way analysis of variance is significant, a comparison of treated groups to control for multiple comparisons will be performed (e.g. Dunnett's test)[2,3]. Where variance is considered significantly

[1] Bartlett, MS. (1937). Properties of sufficiency and statistical tests. *Proceedings of the Royal Statistical Society Series A*, 160, 268-282.
[2] Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics*. 20(3), 482-491.
[3] Dunnett, C.W. (1980). Pairwise multiple comparisons in the unequal variance case. *J. Amer. Statist. Assoc.*, 75, 796-800.

different, groups will be compared using a non-parametric method (e.g. Kruskal-Wallis non-parametric analysis of variance) [1]. When non-parametric analysis of variance is significant, a comparison of treated groups to control will be performed (e.g. Dunn's test) [2].

If warranted by sufficient group sizes, the incidence of clinical observations may be evaluated through sequential application of a trend test[3]. Other procedures will be used if appropriate, and will be described in the final report.

Statistical analysis will be conducted using one or more of the following software applications: Provantis® version 9, Tables and Statistics, Instem LSS, Staffordshire UK; INSTAT or Prism Biostatistics, Graph Pad Software, San Diego, CA; Statview, version 5, SAS Institute Inc.; and SigmaStat, version 2. Other statistical methods will be used if appropriate, at the time of analysis, and described in the final report.

12.B Statistical Methods (Clinical Pathology)

Significance will be judged at a probability value of $p < 0.05$. Males and females will be analyzed separately (Provantis™ version 8, Tables and Statistics, Instem LSS, Staffordshire UK).

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Clinical Pathology*	Levene's[4] test for homogeneity and Shapiro-Wilk[5] test for normality	One-way analysis of variance followed with Dunnett's test	Transforms of the data to achieve normality and variance homogeneity will be used. The order of transforms attempted will be log, square root, and rank-order. If the log and square root transforms fail, the rank-order will be used.

* When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity was reported as >1.100, 1.100 is used for any calculation performed with that specific gravity data.

Other statistical methods will be used if appropriate, at the time of analysis. The statistical methods used will be described in the final report.

13. FINAL REPORT

A signed study report will be provided to the Sponsor. This report will include, but not be limited to, the following information:

- individual animal data (and averages where appropriate) for actual concentration of test substance received; time of observation of each abnormal sign and its subsequent course;
- body weights, food consumption and food efficiency values;
- ophthalmological assessments;

[1] Kruskal, W.H., & Wallis, W.A. (1952). Use of ranks in one-criterion variance analysis. *J. Amer. Statist. Assoc.*, 47, 583-621.
[2] Dunn, O.J. (1964). Multiple contrasts using rank sums. *Technometrics*, 6, 241-252.
[3] Agresti, A (2013). *Categorical Data Analysis* (3rd Edition). John Wiley & Sons, Inc. Hoboken, NJ.
[4] Levene, H. (1960). Robust tests for equality of variances. In: I. Olkin et al (Eds), *Contributions to probability and statistics* (pp. 278-292). Palo Alto, CA: Stanford University Press.
[5] Shapiro, S.S. & Wilk, M.B. (1965). An analysis of variance test for normality (complete samples). *Biometrika*, 52(3-4), 591-611.

- hematology, clinical chemistry, coagulation, and urinalysis results;
- organ weights, organ to body weight and organ to brain weight ratios;
- necropsy and pathology findings;
- test substance and dose preparation analysis;
- a compliance statement signed by the Study Director that states that the report accurately reflects the raw data obtained during the performance of the study and that all applicable GLP regulations were followed in the conduct of the study;
- a Quality Assurance statement summarizing QA activities performed for the study.

14. STUDY CONDUCT

14.A Laboratory

In-life portion	Product Safety Labs 2394 US Highway 130 Dayton, NJ 08810
Ophthalmology evaluation	Kristina R. Vygantas, DVM, DACVO 319 Perrineville Rd. Robbinsville, NJ 08691
Clinical chemistry, hematology, coagulation, and urinalysis	Dupont Haskell Global Centers for Health and Environmental Sciences P.O. Box 30 Elkton Road Newark, DE 19714 P.I.: Denise Hoban, BA, MLT, ASCP
Clinical pathology evaluation	Product Safety Labs 2394 US Highway 130 Dayton, NJ 08810 P.I.: Odete Mendes, DVM, PhD, DACVP, DABT
Test substance and dietary analysis	Impossible Foods, Inc 525 Chesapeake Dr. Redwood City, CA 94063 Prospective P.I.: Rachel Fraser, PhD
Histological slide preparation	Histo-Scientific Research Laboratories (HSRL) 5930 Main Street Mount Jackson, VA 22842 P.I. (histology): Craig Zook
Histological slide evaluation	Histo-Scientific Research Laboratories (HSRL) 5930 Main Street Mount Jackson, VA 22842 Prospective P.I.(s) (pathology): David Garlick, DVM, DACVP Laura E. Elcock, DVM, PhD, DACVP Elizabeth H. Hutto, DVM, PhD, DACVP Daphne Vasconcelos, DVM, PhD, DACVP, DABT Allen Singer, DVM, DACVP, DABT

14.B GLP Compliance

This study will be conducted in compliance with the following regulations:

- U.S. FDA GLP: 21 CFR Part 58, 1987

Which is compatible with:

- OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

Clinical pathology evaluation will be conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Good Laboratory Practices.

Analytical chemistry will be performed in conformance with GLP principles in a non-GLP facility.

14.C Test Procedure Guidelines

This study design is based on the following guidelines:

- OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Part 407): Health Effects, Repeated Dose 28-Day Oral Toxicity Study in Rodents (2008).
- US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. *Subchronic Toxicity Studies with Rodents* (2007).

15. QUALITY ASSURANCE

The Quality Assurance Unit (QAU) of PSL has reviewed this protocol for GLP compliance and will conduct in-process inspections of selected procedures during the study. The final report will be audited for agreement with the raw data records and for compliance with the protocol and PSL SOPs.

In addition, PSL QAU will function as lead QA for this study and will monitor QA activities at DuPont Haskell Global Centers for Health and Environmental Sciences and HSRL. For portions of the study conducted by a subcontractor, the QAU for that facility will conduct necessary critical phase inspections and audit respective results and reports for the study phase according to the SOPs of that facility.

The QA Units from DuPont Haskell Global Centers for Health and Environmental Sciences and HSRL will send all GLP audit reports to the Study Director, Study Director's management, and PSL QAU as soon as they are issued.

16. RECORDS TO BE MAINTAINED

The original signed report will be sent to the Sponsor. A copy of the signed report, together with the protocol and all raw data generated at Product Safety Labs, will be maintained in the Product Safety Labs Archives. PSL will maintain these records for a period of at least five years. After this time, the Sponsor of the study will be offered the opportunity to take possession of the records or will be charged an archiving fee for continued archiving by PSL.

The following records will be maintained:

A. Information on test substance will include but not be limited to the following:

Storage	Dietary analysis
Usage	Test substance analysis
Disposition	

B. Information on animals will include, but not be limited to the following:

Receipt, date of birth	Clinical observations
Initial health assessment	Histopathology data
Dosing	Individual necropsy records
Body weights	Organ weights
Food consumption	Ophthalmologic evaluations
Hematology, clinical chemistry, coagulation, urinalysis data	

C. All other records that would demonstrate adherence to the protocol.

Raw data related to hematology and clinical chemistry evaluations will be maintained by Product Safety Labs and/or DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, DE. Prepared slides and pathology data will be maintained by Product Safety Labs and/or by HSRL, 5930 Main Street, Mount Jackson, VA, 22842. Test substance and dietary analysis data will be maintained by Impossible Foods, Inc. 525 Chesapeake Dr. Redwood City, CA 94063.

17. PROTOCOL AMENDMENTS AND DEVIATIONS

All amendments to this protocol and the reasons therefore shall be documented, signed by the Study Director, dated and maintained with the raw data and protocol. Any deviations from this protocol will be recorded in the raw data and documented in the final report.

18. DISPOSITION OF TEST SUBSTANCE

A reserve sample of the test substance and records of sample disposition will be maintained at Product Safety Labs. All remaining test substance will be retained for at least one year from receipt, unless otherwise specified by the Sponsor. All remaining test substance will be returned to the Sponsor unless otherwise directed.

Product Safety Labs

28-Day dietary Study in rats
Protocol # P703.01 IMP
PSL ID: 160720-5R
Study No: 43166

19. PROTOCOL APPROVAL

Signature: (b) (6)
Rachel Fraser, PhD
Sponsor Representative
Impossible Foods, Inc.
Date: 9/16/16

Signature: (b) (6)
Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs
Date: 9/21/16

Signature: (b) (6)
Odete Mendes, DVM, PhD, DACVP, DABT
Director of Toxicology and Pathology
Product Safety Labs
Date: 16 Sep 16

20. PROTOCOL REVIEW:

Signature: (b) (6)
Rhonda S. Krick, BS
Quality Assurance Director
Product Safety Labs
Date: Sep 16, 2016

New Issue: 09/16/16

Product Safety Labs

PROTOCOL AMENDMENT

SOY LEGHEMOGLOBIN PREPARATION:
A 28-DAY DIETARY STUDY IN RATS

PROTOCOL NO.: P703.01 IMP **AMENDMENT NO.:** 1

STUDY NO.: 43166 **PSL Sample IDs:** 160720-5R

PROTOCOL SECTION (**change from**): **11.F Body Weight and Body Weight Gain**

Individual body weights will be recorded at least two times during acclimation. Test animals will be weighed on Day 0 (prior to study start) and approximately weekly thereafter (intervals of 7 days ± 1). Decedents need not be weighed. Body weight gain will be calculated for selected intervals and for the study overall.

PROTOCOL SECTION (**change to**): **11.F Body Weight and Body Weight Gain**

Individual body weights will be recorded at least two times during acclimation. Test animals will be weighed on Day 0 (prior to study start) and approximately weekly thereafter (intervals of 7 days ± 1). **The animals will also be weighed prior to sacrifice in order to calculate organ to body weight ratios.** Decedents need not be weighed. Body weight gain will be calculated for selected intervals and for the study overall.

REASON: Terminal body weight was not included in the protocol.

EFFECTIVE DATE: September 28, 2016

(b) (6)

9/28/16

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

Date

Product Safety Labs

PROTOCOL AMENDMENT

SOY LEGHEMOGLOBIN PREPARATION:
A 28-DAY DIETARY STUDY IN RATS

PROTOCOL NO.: P703.01 IMP

AMENDMENT NO.: 2

STUDY NO.: 43166

PSL NO.: 160720-5R

PROTOCOL SECTION: 14.A. Laboratory

Change from:

Histological slide evaluation	Histo-Scientific Research Laboratories (HSRL) 5930 Main Street Mount Jackson, VA 22842 Prospective P.I.(s) (pathology): David Garlick, DVM, DACVP Laura E. Elcock, DVM, PhD, DACVP Elizabeth H. Hutto, DVM, PhD, DACVP Daphne Vasconcelos, DVM, PhD, DACVP, DABT Allen Singer, DVM, DACVP, DABT

Change to:

Histological slide evaluation **(Change in bold)**	Histo-Scientific Research Laboratories (HSRL) 5930 Main Street Mount Jackson, VA 22842 Prospective P.I.(s) (pathology): David Garlick, DVM, DACVP Laura E. Elcock, DVM, PhD, DACVP Elizabeth H. Hutto, DVM, PhD, DACVP Daphne Vasconcelos, DVM, PhD, DACVP, DABT Allen Singer, DVM, DACVP, DABT **Daniel G. Branstetter, DVM, PhD, DACVP**

EFFECTIVE DATE: November 1, 2016

(b) (6)

12/23/16

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

Date

Product Safety Labs

PROTOCOL AMENDMENT

SOY LEGHEMOGLOBIN PREPARATION:
A 28-DAY DIETARY STUDY IN RATS

PROTOCOL NO.: P703.01 IMP

AMENDMENT NO.: 3

STUDY NO.: 43166

PSL NO.: 160720-5R

PROTOCOL SECTION: 11.I

Add to section 11.I.

11.I.4 Histopathology Peer Review

A histopathology peer review of female reproductive organs will be performed for all female rats. The peer review pathologist will be Karen Regan, DVM, DABT, DACVP form Regan Path/Tox Services, Inc, 1457 Township Road 853, Ashland, OH 44805. A peer review statement will be inserted in the final study report.

EFFECTIVE DATE: June 1, 2017

(b) (6)

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

June 1, 2017
Date

APPENDIX B: FEED, WATER, AND SEROLOGY ANALYSES

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

APPENDIX B (cont.): FEED

2016C

ENVIGO

Teklad Certified Global 16% Protein Rodent Diet

Lot Number	2016C-080216MA
Date of Manufacture	08/02/16
Report Date	08/16/16

Analysis	Result (%)
Proximate Analysis	
Protein	16.40
Fat	3.83
Fiber	2.96
Moisture	10.33
Ash	4.74
Calcium	0.94
Phosphorus	0.63

Laboratory Diet Certification Report

The following data is a consolidation of results obtained from one or more independent testing laboratories. The actual laboratory results are available upon request.

(b) (6) [redacted] I have reviewed this document 2016.08.16 12:37:20 -05'00'

Analysis	Result	Units	Established Maximum Concentration
Heavy Metals			
Arsenic	0.13	ppm	1.00
Cadmium	< 0.10	ppm	0.50
Lead	< 0.20	ppm	1.50
Mercury	< 0.05	ppm	0.20
Selenium	0.22	ppm	0.50
Mycotoxin			
Aflatoxin B1, B2, G1, G2	< 5.00	ppb	5.00
Chlorinated Hydrocarbons			
Aldrin	< 0.01	ppm	0.03
Lindane	< 0.01	ppm	0.05
Chlordane	< 0.01	ppm	0.05
DDT & related substances	< 0.03	ppm	0.15
Dieldrin	< 0.02	ppm	0.03
Endrin	< 0.02	ppm	0.03
Heptachlor	< 0.01	ppm	0.03
Heptachlor Epoxide	< 0.01	ppm	0.03
Toxaphene	< 0.10	ppm	0.15
PCB's	< 0.10	ppm	0.15
a-BHC	< 0.01	ppm	0.05
b-BHC	< 0.01	ppm	0.05
d-BHC	< 0.01	ppm	0.05
Hexachlorobenzene	< 0.01	ppm	0.03
Mirex	< 0.01	ppm	0.02
Methoxychlor	< 0.05	ppm	0.50
Organophosphates			
Thimet	< 0.16	ppm	0.50
Diazinon	< 0.14	ppm	0.50
Disulfaton	< 0.15	ppm	0.50
Methyl Parathion	< 0.14	ppm	0.50
Malathion	< 0.14	ppm	0.50
Parathion	< 0.12	ppm	0.50
Thiodan	< 0.02	ppm	0.50
Ethion	< 0.14	ppm	0.50
Trithion	< 0.15	ppm	0.50

Envigo Teklad Diets + Madison WI + + tekladinfo@envigo.com (800) 483-5523

APPENDIX B (cont.): WATER

In June 2015, water was analyzed for contaminants.

LABORATORY: PRECISION ANALYTICAL SERVICES, INC.
2161 Whitesville Road
Toms River, NJ 08755

Results of water analysis for possible contaminants were acceptable within regulatory standards.

Specialists in Drinking Water Testing Technologies ■ Residential ■ Industrial ■ Municipal

[illegible] Whitesville Road Toms River, NJ [illegible] Phone 732-914-1515 Fax 732-914-1516

CERTIFICATE OF ANALYSIS

Customer : Product Safety Labs
2394 Route 130
Dayton, NJ 08810

Project ID : 2nd Quarter
PAS Project ID P16-3141

Matrix : Drinking Water
Report Date : 6/28/2016

PAS Sample ID	Client ID	Analyses	Results	Units	PQL	MDL	MCL	Method	Date Sampled	Date Analyzed
P16-3141-01	Room #7	Copper	ND	mg/L	0.05	0.0185	1.30	SM 3111 B	6/21/16 11:20	6/27/16 16:33
P16-3141-01	Room #7	Zinc	ND	mg/L	0.025	0.0092	5.00	SM 3111 B	6/21/16 11:20	6/28/16 13:34
P16-3141-01	Room #7	Lead	ND	mg/L	0.002	0.000462	0.005	SM 3113 B	6/21/16 11:20	6/23/16 15:15
P16-3141-01	Room #7	E. Coli / Colilert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9223 B	6/21/16 11:20	6/21/16 16:55
P16-3141-01	Room #7	Total Coliform / Colilert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9223 B	6/21/16 11:20	6/21/16 16:55
P16-3141-02	Room #10	Copper	ND	mg/L	0.05	0.0185	1.30	SM 3111 B	6/21/16 11:25	6/27/16 16:35
P16-3141-02	Room #10	Zinc	ND	mg/L	0.025	0.0092	5.00	SM 3111 B	6/21/16 11:25	6/28/16 13:36
P16-3141-02	Room #10	Lead	ND	mg/L	0.002	0.000462	0.005	SM 3113 B	6/21/16 11:25	6/23/16 15:19
P16-3141-02	Room #10	E. Coli / Colilert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9223 B	6/21/16 11:25	6/21/16 16:55
P16-3141-02	Room #10	Total Coliform / Colilert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9223 B	6/21/16 11:25	6/21/16 16:55
P16-3141-03	Room #29, Pressure Station	Copper	ND	mg/L	0.05	0.0185	1.30	SM 3111 B	6/21/16 11:35	6/27/16 16:38
P16-3141-03	Room #29, Pressure Station	Zinc	ND	mg/L	0.025	0.0092	5.00	SM 3111 B	6/21/16 11:35	6/28/16 13:39
P16-3141-03	Room #29, Pressure Station	Lead	ND	mg/L	0.002	0.000462	0.005	SM 3113 B	6/21/16 11:35	6/23/16 15:24
P16-3141-03	Room #29, Pressure Station	E. Coli / Colilert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9223 B	6/21/16 11:35	6/21/16 16:55
P16-3141-03	Room #29, Pressure Station	Total Coliform / Colilert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9223 B	6/21/16 11:35	6/21/16 16:55
P16-3141-04	Sipper Bottle	Total Coliform	ND	Col/100mL	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9222 B	6/21/16 11:40	6/22/16 11:20
P16-3141-05	Sipper Top	Total Coliform	NC Interference ***	Col/100mL	1 Col/100mL	1 Col/100mL	0 Col/100mL	SM 9222 B	6/21/16 11:40	6/22/16 11:20

Except for the parameters tested, PAS makes no representation as to the fitness or quality of the water sample taken.

*** Non Coliform Bacteria growth was found to be Confluent and may interfere with the growth of Total Coliform Bacteria. The result is invalidated and resampling is required. (A)

NC = Non-Coliform Bacteria
MCL = Maximum Contaminant Level
PQL = Practical Quantitation Limit
MDL = Minimum Detection Limit
ND = Analyzed for but not detected
B = Compound found in blank and sample
E = Concentration exceeds calibration range
J = Estimated result
* = Internal Action Level

All samples are analysed in accordance with New Jersey Department of Environmental Protection protocols.

Mark D. Fettaluca, Lab. Director

(A) SCP 508 Dev. testing not repeated on sipper top CM 7/6/16
Room 13 faucet not analyzed due to room being out of service (b) (6) 7/7/16

Animals are no longer given water from unfilter source (Nordstrom)
Missing sampling at room 13 has no impact.
Sipper bottle tested OK, no need to test sipper top (tube)
(b) (6) 7/7/16

OK (b) (6)
07/07/16
MZ 07/07/16

APPENDIX B (cont.): SEROLOGY

In October 2016, serology from sentinel animals residing in Room #15, which also housed the study animals, was obtained from collected blood serum for a battery of common viral and microbiologic pathogens.

The sentinel animals along with the test animals were in Room #34 from September 28, 2016, through October 28, 2016, for the duration of the study. Blood samples were collected on October 28, 2016.

LABORATORY: IDEXX BioResearch
4011 Discovery Drive
Columbia, MO 65201

Results of the serology analyses for sentinel animals corresponding with this study are reported as samples 257M 10.28.16, 268M 10.28.16, and 316F 10.28.16. All samples were negative for microbial antibodies.

IDEXX BioResearch

FINAL REPORT OF LABORATORY EXAMINATION

4011 Discovery Drive, Columbia, MO 65201
1-800-669-0825 1-573-499-5700
idexxbioresearch@idexx.com www.idexxbioresearch.com

IDEXX BioResearch Case # 30789-2016

Received: 11/15/2016
Completed: 11/16/2016

Submitted By

Mithila Shitut
Product Safety Labs
2394 US Highway 130
Dayton, NJ 08810

Phone: 732-438-5100 ext. 1558
Email: MithilaShitut@productsafetylabs.com

Specimen Description

Species: rat
Description: Opti-Spot strip(s)
Number of Specimens/Animals: 3

Purchase Order #: P1602593UDC1

Client ID	Investigator	Room #	Strain (Breed)	Sex	Age	Study Number
257M 10.28.16	Mithila Shitut	15	CD/CRL	M	3m	43166
288M 10.28.16	Mithila Shitut	15	CD/CRL	M	3m	43166
316F 10.28.16	Mithila Shitut	15	CD/CRL	F	3m	43166

Services/Tests Performed: Primary Serology Profile

Serologic evaluation for antibodies to: H1, KRV, RCV/SDAV, RMV, RPV, RTV

Summary: All test results were negative.

If you have questions, please call our toll free number at 1-800-669-0825 or e-mail us at idexxbioresearch@idexx.com.

SEROLOGY SUMMARY

	257M 10.26.16	208M 10.26.16	316F 10.26.16
RPV	-	-	-
RMV	-	-	-
KRV	-	-	-
H1	-	-	-
RCV/SDAV	-	-	-
RTV	-	-	-
Rat IgG	N	N	N

Legend: + = positive - = negative blank = test not performed EQ = equivocal HE = hemolysis precluded testing I = insufficient W = weak positive WB = Western Blot confirmatory analysis pending NS = non-specific reactivity N = normal IgG L = less than normal IgG

IDEXX BioResearch
FINAL REPORT OF LABORATORY EXAMINATION
4011 Discovery Drive, Columbia, MO 65201
1-800-669-0825 1-573-499-5700
idexxbioresearch@idexx.com www.idexxbioresearch.com

IDEXX BioResearch Case # 30789-2016

Received: 11/15/2016
Completed: 11/16/2016

SEROLOGY DETAILS

	Baseline	257M 10.28.16	268M 10.28.16	316F 10.28.16
RPV				
RPV purified virus	MFI > 2.000	-	-	-
NS1[1]	MFI > 3.750	-	-	-
RMV				
RMV VP2 recombinant	MFI > 2.000	-	-	-
NS1[1]	MFI > 3.750	-	-	-
KRV				
KRV purified virus	MFI > 2.500	-	-	-
NS1[1]	MFI > 3.750	-	-	-
H1				
H1 purified virus	MFI > 1.750	-	-	-
NS1[1]	MFI > 3.750	-	-	-
RCV/SDAV				
RCV/SDAV purified virus	MFI > 3.750	-	-	-
RCV/SDAV Spike	MFI > 3.750	-	-	-
RTV				
RTV purified virus	MFI > 2.000	-	-	-
TMEV purified virus	MFI > 2.000	-	-	-

NS1[1]: NS1 protein is highly conserved among rodent parvoviruses and thus serves as a generic assay for parvovirus seroconversion.

Legend: + = positive - = negative blank = test not performed EQ = equivocal HE = hemolysis precluded testing I = insufficient W = weak positive WB = Western Blot confirmatory analysis pending NS = non-specific reactivity N = normal IgG L = less than normal IgG

Positive MFI results are reported as "+" followed by a number from 1 to 33 in thousands rounded off to the nearest thousand.

If you have questions, please call our toll free number at 1-800-669-0825 or e-mail us at idexxbioresearch@idexx.com

APPENDIX C: CERTIFICATES OF ANALYSIS

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

Product Safety Labs

CERTIFICATE OF ANALYSIS

Product: Soy Leghemoglobin Preparation

Lot #: PP-PGM2-16-088-301

PSL Reference No.: 160720-5R

Date of Analysis: August 16, 2016

Result:

Soy Leghemoglobin – 48.82%

Approval: (b) (6) [redacted] — 9/17/16
Date

Analytical Services
Product Safety Labs

QA Release: (b) (6) [redacted] — Sep 14, 2016
Date

Rhonda Krick, B.S.
Quality Assurance
Product Safety Labs

This material was analyzed in compliance with Good Laboratory Practice (40 CFR 160) standards. Data are reported in PSL GLP Study No. 43682

PRODUCT SAFETY LABS
2394 US Highway 130
Dayton, NJ 08810
USA

732-438-5100
psl@productsafetylabs.com
www.productsafetylabs.com

APPENDIX D: CHEMICAL ANALYSIS

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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Project Title:
Analysis of Samples from Study:
Soy Leghemoglobin Preparation: A 28-DAY DIETARY STUDY IN RATS

Sponsor
Impossible Foods, Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

ANALYTICAL REPORT

Test Substance:
160720-5R

Author:
Pavel A. Aronov, PhD

Analytical Report Completion Date:
December 7, 2016

Performing Laboratory:

Analytical Services:
Impossible Foods
525 Chesapeake Dr.
Redwood City, CA, 94063

Project Identification Number:
Impossible Foods Study Number IF-43166

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Soy Leghemoglobin Preparation

This analysis was conducted in a non-GLP certified facility. Method validation and sample analysis were performed and documented according to GLP. Characterization of reference substance was documented according to GLP.

(b) (6)

Principal Investigator: [redacted] Date: 12/7/2016

Name of Signer: Pavel A. Aronov, PhD

Name of Company: Impossible Foods

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SIGNATURE

Soy Leghemoglobin Preparation

I, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

(b) (6)

Pavel A. Aronov, PhD
Principal Scientist
Impossible Foods

12/7/2016
Date

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STUDY INFORMATION

Protocol No.:	IF-43166
Test Substance:	Soy Leghemoglobin Preparation Lot/Batch #: PP-PGM2-16-088-301
Physical Description:	Red/Brown Powder
Date Test Substance Received:	October 11, 2016 and October 25, 2016
PSL Reference Nos.:	160720-5R
PSL Study Number:	43166
Sponsor:	Impossible Foods, Inc.
Dates of Analysis:	
Analytical Principal Investigator:	Pavel A. Aronov, PhD
Primary Chemists:	Puja Agrawal, MS
	Rachel Fraser, PhD

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1. SUMMARY

This report presents the dietary mixture and test substance analysis phase of PSL Study Number 43166: Soy Leghemoglobin Preparation: A 28-DAY DIETARY STUDY IN RATS. Samples were collected at various intervals for neat test substance stability (NT), stability in the dietary mixture (SA), homogeneity (HO), and concentration verification (CV) and transferred to the Analytical laboratory of Impossible Foods. This method was validated in terms of linearity, specificity, precision, and accuracy. All samples were received frozen and were maintained frozen prior to extraction.

Samples (BO – Both Male and Female diets, MA – Male diet, FE – Female diet):

Neat test substance for Stability: Week 1, Week 3, and Week 4

NT 1 A
NT 2 A
NT 3 A

Dietary mixture samples for Stability (Days 0, 4, 7 and 10):

SA0 1A BO	SA7 17A FE	SA0 6A MA
SA4 8A BO	SA10 24A FE	SA4 13A MA
SA7 15A BO	SA0 4A MA	SA7 20A MA
SA10 22A BO	SA4 11A MA	SA10 27A MA
SA0 2A MA	SA7 18A MA	SA0 7A FE
SA4 9A MA	SA10 25A MA	SA4 17A FE
SA7 16A MA	SA0 5A FE	SA7 21A FE
SA10 23A MA	SA4 12A FE	SA10 28A FE
SA0 3A FE	SA7 19A FE	
SA4 10A FE	SA10 26A FE	

Initial (Day 0) Dietary Samples for Concentration Verification: and Homogeneity (T = top, M = middle, B = bottom):

HO 1 A M BO	HO 11 A T FE
HO 2 A T MA	HO 12 A M FE
HO 3 A M MA	HO 13 A B FE
HO 4 A B MA	HO 14 A T MA
HO 5 A T FE	HO 15 A M MA
HO 6 A M FE	HO 16 A B MA
HO 7 A B FE	HO 17 A T FE
HO 8 A T MA	HO 18 A M FE
HO 9 A M MA	HO 19 A B FE
HO 10 A B MA	

Intermediate (Day 7) Dietary Samples for Concentration Verification:

CV 1 A BO	CV 4 A MA
CV 2 A MA	CV 5 A FE
CV 3 A FE	CV 6 A MA

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CV 7 A FE

Final (Day 21) Dietary Samples for Concentration Verification:

CV 8 A BO
CV 9 A MA
CV 10 A FE
CV 11 A MA
CV 12 A FE
CV 13 A MA
CV 14 A FE

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2. PROCEDURE FOR THE DETERMINATION OF SOY LEGHEMOGLOBIN PREPARATION BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

A. Reference Standard

Note: The neat test substance was used as the reference standard. No purity correction was applied. Results were reported as test substance concentration (versus active ingredient concentration).

Name: Soy Leghemoglobin Preparation
Lot/Batch #: PP-PGM2-16-088-301
PSL No.: 160720-5R
Purity: 48.82%
Exp. Date: March 2017
Supplied by: Impossible Foods, Inc

B. Method Validation

Linearity, system suitability, specificity, precision, and accuracy (spike recovery) determinations were performed prior to analysis.

Stock Standard Solution: A standard solution was prepared by weighing 0.1 grams of reference standard into a 50 mL polypropylene tube, diluting with 25 g of Lysis Reagent, shaking for 60 minutes, and mixing well.

2.B.1 Detector Linearity: The linearity of detector response was assessed using reference substance solutions targeted to bracket the expected concentrations for the analyte.

Linearity Standard Preparation: Five standard solutions with concentrations ranging from approximately 0.125 to 2 mg/mL (LIN 1 - LIN 5) were prepared by preparing individual dilutions of the stock standard solution in Lysis Reagent by weight and mixing well. Linearity solution shelf life is 3 days at 4C or 12 months at -80C.

Linear regression of the analyte peak gave coefficients of determination (R^2) of 0.9977 - 1.0000, which were considered acceptable.

2.B.2 System Suitability: Five replicate injections of the mid-point linearity solution (LIN 3-1) produced relative standard deviations for this study of 0.2% - 1.5% for peak response and 0.0% - 0.2% for retention time.

2.B.3 Specificity: Specificity was demonstrated by the absence of significant interferences in replicate linearity (LIN 1-A) and control feed samples (HO 1 AM-1). Background was <5% of the lowest standard signal.

2.B.4 Accuracy (Spike recovery) and Precision:

Duplicate QC stock solutions were prepared by weighing approximately 0.5 gram of a control sample (HO 1 AM) into separate 50 mL polypropylene centrifuge tubes, pipetting 1.25 mL (QC Low) or 2.5 mL (QC High) of STD1 stock standard solution, and adding 8.75 mL (QC High) or 7.5 mL (QC High) of Lysis Reagent into each tube. Each mixture was capped and placed in a mechanical shaker for 60 minutes. The solutions were allowed to settle for 30 minutes and filtered using a 0.2μm 96-well filter

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plates. Filtrate was collected in 96-well conical bottom plate for HPLC analysis.

Chromatography of the working QC solutions demonstrated accuracy (% recovery) to be 88.2% - 97.7% for QC Low and 87.2 – 92.6% for QC High. The %RSD was 0.3% - 3.7% for QC Low and 0.6% - 1.2% for QC High for precision.

C. Analysis by High Performance Liquid Chromatography (HPLC)

2.C.1 Standard Preparation: The linearity solutions were injected with every sequence and were used for interpolation of assay results. An example result is shown in 2.B.1.

Note: All diet samples were removed from the freezer and allowed to equilibrate to room temperature before weighing.

2.C.2 Test Sample Preparation for Neat Test Substance: Samples were prepared in triplicate. Approximately 0.1 g of the test substance was weighed into 50 mL polypropylene centrifuge tubes, diluted with 25 g lysis reagent, and placed in a mechanical shaker for 60 minutes. Secondary dilutions were performed as necessary. Samples were mixed well and filtered using a 0.2µm 96-well filter plates. Filtrate was collected in 96-well conical bottom plate for HPLC analysis. Filtrate shelf life is 3 days at 4C or 12 months at -80C.

2.C.3 Sample Preparation for Dietary Samples: Each sample was prepared in triplicate. Approximately 0.5 g of a sample was weighed into a 50 mL polypropylene centrifuge tube and diluted with Lysis Reagent as necessary (higher concentration samples had a higher dilution). The solution was capped and placed in a mechanical shaker for 60 minutes. The solutions were allowed to settle for 30 minutes and filtered using a 0.2µm 96-well filter plates. Filtrate was collected in 96-well conical bottom plate for HPLC analysis. Filtrate shelf life is 3 days at 4C or 12 months at -80C.

2.C.4 Analysis: At the beginning of the analysis, the instrument was equilibrated until it gave a stable, consistent baseline. The standards and samples were injected at consistent time intervals in order to maintain a steady baseline. A solvent blank and standards were run; all samples were injected in singlet.

2.C.5 Calculations: Results were determined as follows:

$$\text{Calculated Conc (mg/g)} = \frac{\text{Peak Area - Intercept}}{\text{Slope}}$$

$$\text{Dose Conc (ppm)} = \frac{\text{Calc. Conc (mg/g) x Extraction Buffer Wt. (g) x 1000}}{\text{Sample weight (g)}}$$

$$\text{Theoretical Spike Conc. (mg/g)} = \frac{\text{Wt. of Std. (g)}}{\text{Extraction Buffer Wt. (g)}} \text{ x Std. Conc. (mg/g)}$$

Final Conc (mg/g) = Theoretical Spike Conc (mg/g) x Wt of Sample Aliquot (g) / Final Wt (g)

$$\text{\% Recovery} = \frac{\text{Calc. Conc. (mg/g)}}{\text{Final Conc.(mg/g)}} \text{ x 100}$$

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$$\%\ \text{Signal / Background} = \frac{\text{Avg. LIN 1-A area response}}{\text{Avg. Control area response}} \times 100$$

$$\%\ \text{Target} = \text{Dose Conc. (ppm) / Corrected Dose Level (ppm)} \times 100$$

3. RESULTS

A summary of the analytical chemistry results is presented in Table 1A-D. HPLC operating conditions are presented in Table 2. The analytical method passed all validation parameters (linearity, system suitability, specificity, precision, and accuracy) and results are reported in Table 3. Detailed results of stability analysis, homogeneity analysis, and concentration verification are presented in Tables 4-5. Chromatograms are maintained in the raw data but were not included in this report.

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TABLE 1A: CHEMICAL ANALYSIS RESULTS

Results for Neat Test Substance Stability Samples

Sampling Day	Measured Recovery (%)	% Change[1]	Overall Stability (%)
Day 0 (Initial)	94.96%	0.00%	100.00%
Day 14 (Middle)	95.29%	0.35%	100.35%
Day 21 (Final)	90.88%	-4.30%	95.70%

[1] $\frac{\text{Final Sample} - \text{Initial Sample}}{\text{Initial Sample}} \times 100$

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TABLE 1B: CHEMICAL ANALYSIS RESULTS

Results for Dietary Stability of Initial Samples

Day[1]	Group	Target Concentration (ppm)	Measured Concentration (ppm)	% of Target[2]
0	1 (BO)	0	ND	NA
	2 (M)	4373	4508	103.08%
	2 (F)	4711	4645	98.61%
	3 (M)	8746	7951	90.91%
	3 (F)	9422	9034	95.89%
	4(M)	13118	12265	93.50%
	4(F)	14133	12808	90.62%
4	1 (BO)	0	ND	NA
	2 (M)	4373	4207	96.20%
	2 (F)	4711	4471	94.90%
	3 (M)	8746	8238	94.19%
	3 (F)	9422	8918	94.65%
	4(M)	13118	12097	92.22%
	4(F)	14133	13191	93.33%
7	1 (BO)	0	ND	NA
	2 (M)	4373	4202	96.09%
	2 (F)	4711	4468	94.84%
	3 (M)	8746	8200	93.76%
	3 (F)	9422	8728	92.63%
	4(M)	13118	12423	94.70%
	4(F)	14133	13547	95.85%
10	1 (BO)	0	ND	NA
	2 (M)	4373	3968	90.74%
	2 (F)	4711	4693	99.63%
	3 (M)	8746	8453	96.65%
	3 (F)	9422	8836	93.78%
	4(M)	13118	12825	97.77%
	4(F)	14133	13762	97.38%

NA = Not Applicable; ND = Not Detected

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100

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TABLE 1C: CHEMICAL ANALYSIS RESULTS

Results for Homogeneity of Dietary Preparations

Day[1]	Group	Sample Location	Target Concentration (ppm)	Measured Concentration (ppm)	% of Target[2]	Average % of Target	RSD (%)
0	1 (BO)	Middle	0	ND	NA	NA	NA
	2 (M)	Top	4373	4302	98.38%	95.87%	2.92%
		Middle		4061	92.86%		
		Bottom		4215	96.38%		
	2 (F)	Top	4711	4853	103.01%	98.01%	4.77%
		Middle		4583	97.28%		
		Bottom		4416	93.74%		
	3 (M)	Top	8746	8636	98.74%	95.40%	3.09%
		Middle		8145	93.13%		
		Bottom		8250	94.33%		
	3 (F)	Top	9422	9669	102.62%	97.71%	5.50%
		Middle		9284	98.53%		
		Bottom		8666	91.98%		
	4 (M)	Top	13118	12226	93.20%	97.85%	5.24%
		Middle		13558	103.35%		
		Bottom		12724	97.00%		
	4 (F)	Top	14133	14567	103.07%	98.64%	5.57%
		Middle		14183	100.35%		
		Bottom		13072	92.49%		

NA = Not Applicable; ND = Not Detected

[1] Day relative to initial dietary preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100.

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TABLE 1D: CHEMICAL ANALYSIS RESULTS

Results for Concentration Verification of Dietary Preparations

Day[1]	Group	Target Concentration (ppm)	Measured Concentration (ppm)	% of Target[2]
0[3]	1 (BO)	0	ND	NA
	2 (M)	4373	4061	92.86%
	2 (F)	4711	4583	97.28%
	3 (M)	8746	8145	93.13%
	3 (F)	9422	9284	98.53%
	4(M)	13118	13558	103.35%
	4(F)	14133	14183	100.35%
7	1 (BO)	0	ND	NA
	2 (M)	6093	6158	101.06%
	2 (F)	5824	5326	91.45%
	3 (M)	12318	12189	98.96%
	3 (F)	11664	11408	97.81%
	4(M)	18362	19409	105.70%
	4(F)	17567	17238	98.13%
21	1 (BO)	0	ND	NA
	2 (M)	7407	6906	93.24%
	2 (F)	5925	5498	92.80%
	3 (M)	14727	14292	97.05%
	3 (F)	12901	12612	97.76%
	4(M)	21943	20786	94.73%
	4(F)	19281	18829	97.65%

NA = Not Applicable; ND = Not Detected

[1] Days relative to the initial diet preparation.
[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100
[3] As part of the homogeneity analysis.

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TABLE 2: HPLC OPERATING CONDITIONS

Instrument		Agilent 1100 Series HPLC System, with DAD	
Column		Waters Acquity xBridge BEH125 SEC, 7.8 x 150 mm ID 3.5µm	
Flow rate (mL/min)		0.86	
Injection Volume (µL)		25	
Wavelength (nm)		405	
Column Temperature (°C)		Ambient	
Tray Temperature (°C)		4	
Run time (min)	Flow rate (ml/min)	HPLC-Grade Water (%)	50 mM Potassium Phosphate pH 7.4, 5 mM Sodium Chloride (%)
0-14.00 min	0.86	0	100
14.01-19.00 min	0.86	100	0
19.01 to 30.00 min	0.86	0	100

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TABLE 3: METHOD VALIDATION RESULTS

Linearity

(Analyzed on 11/17/2016)

Sample ID	Peak Area	Theoretical Concentration (mg/g)
Lin 1	10.5743	0.1236
	10.7110	0.1239
Lin 2	23.4604	0.2572
	22.9334	0.2509
Lin 3	47.5942	0.5066
	46.4874	0.4962
Lin 4	94.8130	1.0224
	93.6001	0.9964
Lin 5	187.6864	2.0265
	184.2777	1.9985
	Slope:	92.7032
	Intercept:	-0.1151
	Correlation Coefficient (r):	0.9999

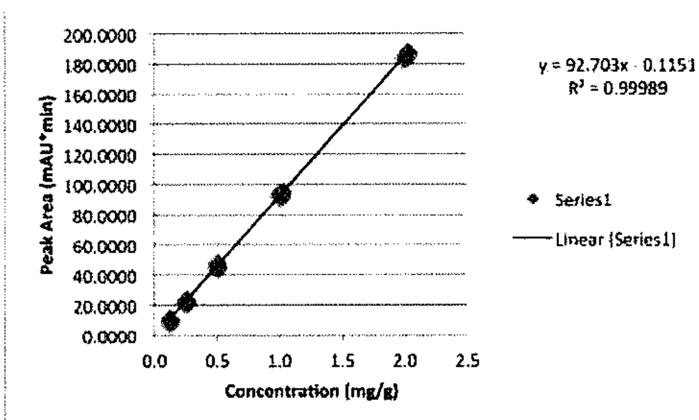

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TABLE 3 (cont.): METHOD VALIDATION RESULTS

System Suitability

(Analyzed on 11/17/2016)

Sample ID	Theoretical Conc. (mg/g)	Retention time (min)	Peak Area
LIN 3-1	0.4962	4.1680	45.1002
		4.1682	44.9289
		4.1687	44.7097
		4.1703	44.3757
		4.1688	44.2105
Average		4.1688	44.6650
STDEV		0.0009	0.3713
%RSD		0.0%	0.8%

Accuracy and Precision

(Analyzed on 11/17/2016)

Sample Name	Theoretical Conc. (mg/g)	Peak Area	Calculated Conc. (mg/g)	% Recovery	Average % Recovery (SD / %RSD)
QC Low	0.5012	45.1037	0.4878	97.3%	97.0% (0.3% / 0.3%)
		44.9771	0.4864	97.0%	
	0.5062	45.4857	0.4919	97.2%	
		45.2369	0.4892	96.6%	
QC High	1.0082	87.1050	0.9409	93.3%	92.6% (0.7% / 0.8%)
		86.7802	0.9373	93.0%	
	1.0086	86.1798	0.9309	92.3%	
		85.6498	0.9252	91.7%	
y = 92.7032 - 0.1151					

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TABLE 3 (cont.): METHOD VALIDATION RESULTS

Specificity (Analyzed on 10/17/2016)

	Peak Area	Specificity
LIN 1-A	11.1192	NA
	11.7481	
HO 1 AM-1	ND	
HO 1 AM-2	ND	
HO 1 AM-3	ND	

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TABLE 4: NEAT TEST SUBSTANCE STABILITY ANALYSIS

Analyzed on 10/27/2016

Day[1]	Sample Name	Sample Weight (g)	Final Conc. (mg/g)	Peak Area	Calculated Conc. (mg/g)	% Recovery	Avg. % Recovery	SD / %RSD
0	NT 1 A	0.1017	0.4974	45.3436	0.4738	95.25%	94.96%	0.0036 / 0.38%
		0.0998	0.4888	44.2652	0.4622	94.55%		
		0.1011	0.4960	45.1470	0.4717	95.08%		
14	NT 2 A	0.1026	0.5017	45.6401	0.4770	95.08%	95.29%	0.0053 / 0.55%
		0.1031	0.5016	45.5543	0.4760	94.91%		
		0.1008	0.4886	44.8581	0.4686	95.89%		
21	NT 3 A	0.1039	0.5087	43.0057	0.4487	88.20%	90.88%	0.0245 / 2.70%
		0.1031	0.5132	45.6832	0.4774	93.02%		
		0.1047	0.5181	45.3258	0.4736	91.41%		
y = 93.1257 + 1.2237								

[1] Days relative to the initial diet preparation.

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TABLE 5: DIETARY MIXTURE SAMPLE ANALYSIS

Study Day 0 (HO BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average	%Target between the strata (Avg. / RSD)
HO 1 A M-1	0.5071	5.0400	0	ND	NA	NA	NA	NA	NA	NA	NA
HO 1 A M-2	0.5011	5.0178		ND	NA	NA			NA		
HO 1 A M-3	0.5091	5.0351		ND	NA	NA			NA		
HO 2 A T-1	0.5221	5.0605	4375	44.2192	0.4500	4449	4302	3.00%	101.75%	98.39%	95.87% ± 2.93%
HO 2 A T-2	0.5204	5.0073		42.4804	0.4406	4191			95.83%		
HO 2 A T-3	0.5051	5.0814		40.9036	0.4241	4267			97.57%		
HO 3 A M-1	0.5071	5.0640		39.6148	0.4110	4110	4063	1.89%	94.02%	92.89%	
HO 3 A M-2	0.5298	5.0739		40.0667	0.4148	3973			90.85%		
HO 3 A M-3	0.5076	5.0686		39.6398	0.4104	4098			93.71%		
HO 4 A B-1	0.4943	5.0630		38.3794	0.3970	4066	4215	4.99%	92.98%	96.38%	
HO 4 A B-2	0.5022	5.0455		*	*	3535			*		
HO 4 A B-3	0.5122	5.1625		42.4020	0.4397	4363			99.78%		
HO 5 A T-1	0.5277	5.0770	4711	47.3590	0.4880	4695	4853	2.67%	99.65%	103.01%	98.01% ± 4.77%
HO 5 A T-2	0.5022	5.0649		47.6758	0.4912	4958			105.23%		
HO 5 A T-3	0.4967	5.1461		46.8567	0.4829	4905			104.13%		
HO 6 A M-1	0.5103	5.0546		45.7853	0.4720	4693	4581	3.01%	99.63%	97.28%	
HO 6 A M-2	0.5150	5.0555		43.7026	0.4509	4426			93.95%		
HO 6 A M-3	0.4991	4.9870		44.9234	0.4633	4629			98.26%		
HO 7 A B-1	0.4997	5.1060		43.7868	0.4517	4553	4410	3.25%	96.64%	93.71%	
HO 7 A B-2	0.4996	5.0504		40.0276	0.4136	4267			90.57%		
HO 7 A B-3	0.5034	5.0170		43.0629	0.4444	4429			94.02%		
HO and MA: y = 94.0590x + 1.0415 FE: y = 98.6434x + 0.7744											

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 0 Cont. (HO BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average	%Target between the strata (Avg. / RSD)
HO 8 A T-1	0.5044	10.1502	8746	31.1902	0.3205	6430	6814	4.97%	73.75%	77.91%	80.45% / 4.03%
HO 8 A T-2	0.5037	10.1210		33.2054	0.3420	6871			78.56%		
HO 8 A T-3	0.5127	10.0718		35.0665	0.3617	7120			81.41%		
HO 9 A M-1	0.5340	10.0477		34.6848	0.3533	6796	6936	4.35%	77.72%	79.31%	
HO 9 A M-2	0.5212	10.0362		34.1460	0.3500	6777			77.49%		
HO 9 A M-3	0.5177	10.1904		36.7414	0.3772	7302			83.49%		
HO 10 A B-1	0.5118	10.1298		37.2761	0.3852	7625	7355	7.08%	87.18%	84.10%	
HO 10 A B-2	0.4921	10.0857		36.3183	0.3750	7687			87.89%		
HO 10 A B-3	0.5299	10.1426		34.3700	0.3522	6754			77.23%		
HO 11 A T-1	0.4995	10.1081	9422	39.6039	0.4093	8133	8401	5.67%	88.44%	90.12%	87.55% / 4.42%
HO 11 A T-2	0.5064	10.0792		39.3279	0.4065	8092			85.88%		
HO 11 A T-3	0.5059	10.0604		44.0646	0.4546	9050			96.05%		
HO 12 A M-1	0.5223	10.0624		43.6492	0.4501	8678	8427	3.70%	92.10%	90.41%	
HO 12 A M-2	0.4906	10.0948		40.3411	0.4148	8535			90.59%		
HO 12 A M-3	0.5129	10.0411		39.8731	0.4121	8067			85.62%		
HO 13 A B-1	0.5200	10.0188		41.4060	0.4276	8239	7830	5.83%	87.44%	83.10%	
HO 13 A B-2	0.5021	10.0527		38.2093	0.3952	7912			83.98%		
HO 13 A B-3	0.5066	10.0546		35.6749	0.3695	7337			77.88%		
HO 14 A T-1	0.5172	15.0007	13118	30.1873	0.3099	9027	9779	7.60%	68.78%	74.54%	77.51% / 5.37%
HO 14 A T-2	0.5146	15.1351		34.7101	0.3579	10528			80.25%		
HO 14 A T-3	0.5112	15.0663		32.2306	0.3319	9782			74.57%		
HO 15 A M-1	0.5110	15.1496		33.2490	0.3428	10328	10369	0.88%	78.73%	78.91%	
HO 15 A M-2	0.5113	15.0406		34.2383	0.3529	10568			79.10%		
HO 15 A M-3	0.4912	15.1132		32.4473	0.3339	10211			77.84%		
HO 16 A B-1	0.5085	15.0909		33.7001	0.3472	10263	10417	1.80%	78.24%	79.41%	
HO 16 A B-2	0.4912	15.1231		32.6994	0.3368	10362			78.99%		
HO 16 A B-3	0.5219	15.2106		35.4266	0.3656	10626			81.00%		
BO and MA: y = 96.0996x + 1.0416 FE: y = 96.6434x - 0.7748											

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 0 Cont. (HO BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average	% Target between the strata
HO 17 A T-1	0.5173	15.0543	14133	38.2878	0.3960	11529	11384	2.21%	81.57%	80.55%	79.37% / 1.39%
HO 17 A T-2	0.5130	14.9814		38.3201	0.3961	11529			81.58%		
HO 17 A T-3	0.4937	15.0079		35.3673	0.3664	11093			78.49%		
HO 18 A M-1	0.5126	15.1448		36.6923	0.3798	11157	11197	3.47%	78.94%	79.22%	
HO 18 A M-2	0.5000	15.1290		34.5308	0.3579	10830			76.63%		
HO 18 A M-3	0.4911	15.1299		36.3798	0.3767	11604			82.11%		
HO 19 A B-1	0.5172	15.1035		38.9280	0.4025	11892	11074	6.49%	84.14%	78.35%	
HO 19 A B-2	0.5001	15.0779		34.5206	0.3578	10788			76.33%		
HO 19 A B-3	0.4926	15.0226		33.3371	0.3458	10542			74.59%		
BO and MA: y = 94.1599x + 1.0416 FE: y = 98.6334x - 0.7748											

NA = Not Applicable; ND = Not Detected

* Excluded due to non-trending result

Cells shaded in gray were re-analyzed on 11/8/2016 and 11/9/2016 due to low signal.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation (HO MA Analyzed on 11/8/2016, HO TE Analyzed on 11/9/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	% RSD	% Target	% Target Average	% Target between the strata (Avg. ± RSD)
HO 8 A T-1	0.5044	10.1502	8740	41.3494	0.4309	8671	9036	5.00%	99.14%	98.74%	95.67% ± 2.97%
HO 8 A T-2	0.5037	10.1210		43.1624	0.4510	9039			103.40%		
HO 8 A T-3	0.5127	10.0918		39.9993	0.4160	8187			93.61%		
HO 9 A M-1	0.5240	10.0477		41.6205	0.4338	8318	8145	3.40%	95.11%	93.13%	
HO 9 A M-2	0.5212	10.0362		38.5999	0.4014	7728			88.17%		
HO 9 A M-3	0.5177	10.1304		41.1521	0.4288	8390			95.99%		
HO 10 A B-1	0.5118	10.3298		41.2484	0.4298	8507	8321	7.00%	97.36%	95.14%	
HO 10 A B-2	0.4921	10.0857		41.1725	0.4290	8792			100.59%		
HO 10 A B-3	0.5289	10.3426		38.4385	0.3996	7663			87.62%		
HO 11 A T-1	0.4995	10.1080	9222	45.5444	0.4759	9686	9669	5.18%	102.81%	102.62%	97.73% ± 5.50%
HO 11 A T-2	0.5064	10.0792		43.5856	0.4502	9139			97.70%		
HO 11 A T-3	0.5085	10.2001		48.8990	0.5113	10180			108.04%		
HO 12 A M-1	0.5222	10.0624		47.0073	0.4926	9402	9281	1.24%	100.34%	98.50%	
HO 12 A M-2	0.4936	10.0948		43.8998	0.4578	9421			99.90%		
HO 12 A M-3	0.5120	10.0131		43.7416	0.4566	8938			94.82%		
HO 13 A B-1	0.5200	10.0188		44.8412	0.4684	9025	8660	3.77%	95.78%	91.98%	
HO 13 A B-2	0.5021	10.0527		41.1713	0.4290	8598			91.15%		
HO 13 A B-3	0.5066	10.0596		40.5455	0.4222	8385			88.99%		
HO 14 A T-1	0.5175	15.0607	13118	40.3516	0.4202	12235	13260	7.06%	93.27%	101.08%	100.48% ± 3.20%
HO 14 A T-2	0.5146	15.1351		45.7343	0.4784	14070			107.26%		
HO 14 A T-3	0.5112	15.0663		43.7994	0.4572	13474			102.72%		
HO 15 A M-1	0.5116	15.1498		44.9781	0.4698	13912	13558	2.31%	106.05%	103.35%	
HO 15 A M-2	0.5113	15.0496		43.7359	0.4568	13444			102.49%		
HO 15 A M-3	0.4942	15.1132		41.7757	0.4355	13317			101.51%		
HO 16 A B-1	0.5085	15.0009		40.9314	0.4264	12604	12724	0.99%	96.08%	97.00%	
HO 16 A B-2	0.4912	15.1231		40.0590	0.4172	12846			97.93%		
HO 16 A B-3	0.5231	15.2106		41.9860	0.4377	12723			96.99%		

$y = 94.1257x + 1.2237$

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 0 Cont. (HO MA Analyzed on 11/8/2016, HO FE Analyzed on 11/9/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average	%Target between the strata
HO 17 A T-1	0.5173	15.0543	14130	47.8680	0.5009	14582	14567	0.32%	103.18%	103.07%	96.64% - 9.57%
HO 17 A T-2	0.5130	14.9814		47.9792	0.5021	14605			103.34%		
HO 17 A T-3	0.4957	15.0379		45.8705	0.4704	14515			102.70%		
HO 18 A M-1	0.5156	15.1428		46.9848	0.4914	14434	14181	1.71%	102.15%	100.35%	
HO 18 A M-2	0.5000	15.1290		44.1394	0.4808	13944			98.66%		
HO 18 A M-3	0.4911	15.1299		44.0586	0.4800	14173			100.27%		
HO 19 A B-1	0.5112	15.1035		41.3844	0.4635	13693	13072	4.71%	96.90%	92.49%	
HO 19 A B-2	0.5081	15.0779		41.2615	0.4132	13060			92.40%		
HO 19 A B-3	0.4928	15.0228		39.2856	0.4068	12461			88.19%		
$y = 93.1257x + 1.2237$											

Cells shaded in gray were re-analyzed on 12/05/2016 due to high %RSD.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation (SA BO MA Analyzed on 10/21/2016, SA FE Analyzed on 10/24/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/mL)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
SA 0-1 A-1	0.4880	4.9092		ND	NA	NA			NA	
SA 0-1 A-2	0.5069	4.9984		ND	NA	NA	NA	NA	NA	NA
SA 0-1 A-3	0.5263	4.9085		ND	NA	NA			NA	
SA 4-8 A-1	0.5051	5.0002		ND	NA	NA			NA	
SA 4-8 A-2	0.4835	4.9194		ND	NA	NA	NA	NA	NA	NA
SA 4-8 A-3	0.4863	4.9915	0	ND	NA	NA			NA	
SA 7-15 A-1	0.4809	4.9244		ND	NA	NA			NA	
SA 7-15 A-2	0.5123	4.9587		ND	NA	NA	NA	NA	NA	NA
SA 7-15 A-3	0.4881	4.9250		ND	NA	NA			NA	
SA 10-22 A-1	0.5285	4.9491		ND	NA	NA			NA	
SA 10-22 A-2	0.5050	4.9289		ND	NA	NA	NA	NA	NA	NA
SA 10-22 A-3	0.5115	4.9702		ND	NA	NA			NA	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA 4-9 A-1	0.4850	4.9178		39.5467	0.4139	4206			96.19%	
SA 4-9 A-2	0.4037	4.9806		37.7820	0.3953	3968	4207	5.21%	91.20%	96.20%
SA 4-9 A-3	0.5068	4.9570		41.1991	0.4525	4429			101.21%	
SA 7-16 A-1	0.4970	4.9780	4573	39.3080	0.4114	4113			94.06%	
SA 7-16 A-2	0.5023	4.9007		40.2228	0.4211	4155	4202	2.80%	95.02%	96.10%
SA 7-16 A-3	0.5176	4.9378		41.3602	0.4546	4337			90.17%	
SA 10-23 A-1	0.5019	5.0154		39.1195	0.4096	4090			93.61%	
SA 10-23 A-2	0.5042	4.9900		38.4588	0.4024	3980	3966	1.56%	91.60%	90.74%
SA 10-23 A-3	0.5045	5.0001		36.9239	0.3863	3828			87.54%	

BO and MA: $y = 94.7024x + 0.3440$ FE: $y = 94.3266x + 0.4280$

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FF Analyzed on 10/24/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
SA 0-3 A-1	0.5260	5.0218	4711	46.3028	0.4863	4697	4645	1.93%	99.70%	98.61%
SA 0-3 A-2	0.5102	4.9969		44.1541	0.4636	4542			96.41%	
SA 0-3 A-3	0.4980	5.0600		44.0296	0.4622	4697			99.71%	
SA 4-10 A-1	0.4967	4.9941		42.3142	0.4441	4524	4471	1.74%	96.03%	94.90%
SA 4-10 A-2	0.5008	4.9027		41.8842	0.4395	4381			93.01%	
SA 4-10 A-3	0.5016	5.0280		42.8506	0.4495	4500			95.53%	
SA 7-17 A-1	0.5180	5.0069		42.8733	0.4500	4347	4468	2.44%	92.27%	94.84%
SA 7-17 A-2	0.5057	5.0416		42.9561	0.4509	4498			95.49%	
SA 7-17 A-3	0.5296	5.0191		45.5214	0.4781	4558			96.75%	
SA 10-24 A-1	0.5134	4.9918		46.1824	0.4851	4716	4693	5.01%	100.11%	99.63%
SA 10-24 A-2	0.5069	4.9800		47.5344	0.4993	4916			104.35%	
SA 10-24 A-3	0.4960	5.0624		41.7004	0.4375	4448			94.41%	
SA 0-4 A-1	0.5215	10.1290	8746	37.6933	0.3942	7656	7448	4.55%	87.53%	85.16%
SA 0-4 A-2	0.4894	10.0902		35.4056	0.3702	7633			87.27%	
SA 0-4 A-3	0.5177	10.0873		34.7136	0.3629	7057			80.69%	
SA 4-11 A-1	0.4929	10.0017		36.1305	0.3780	7732	7478	2.90%	88.41%	85.50%
SA 4-11 A-2	0.5228	10.0884		36.3528	0.3802	7337			83.89%	
SA 4-11 A-3	0.5140	10.0994		35.8883	0.3753	7364			84.20%	
SA 7-18 A-1	0.5121	10.0562		34.9482	0.3654	7175	7270	1.20%	82.04%	83.12%
SA 7-18 A-2	0.5158	10.0539		37.0016	0.3880	7419			84.83%	
SA 7-18 A-3	0.5091	10.0922		34.8172	0.3640	7216			82.50%	
SA 10-25 A-1	0.5029	10.1052		37.3867	0.3911	7811	7518	6.00%	89.31%	85.96%
SA 10-25 A-2	0.5153	10.1106		33.7151	0.3524	6919			79.11%	
SA 10-25 A-3	0.5203	10.1068		38.4896	0.4028	7824			89.46%	

BO and MA: $y = 94.7074x + 0.5440$ FF: $y = 94.3266x + 0.4283$

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FF Analyzed on 10/24/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
SA 0-5 A-1	0.4950	10.1258	9422	38.1442	0.3998	8179	7207	11.70%	86.81%	76.49%
SA 0-5 A-2	0.5198	10.1349		33.1659	0.3473	6771			71.86%	
SA 0-5 A-3	0.5016	10.0224		31.9203	0.3339	6671			70.80%	
SA 4-12 A-1	0.5175	10.1398		39.5024	0.4149	8121	8102	1.77%	86.19%	85.99%
SA 4-12 A-2	0.4992	9.9998		39.2047	0.4311	8235			87.40%	
SA 4-12 A-3	0.5180	10.1180		38.8221	0.4070	7950			84.38%	
SA 7-19 A-1	0.5260	10.0854		39.8415	0.4178	7992	7910	0.77%	84.80%	83.95%
SA 7-19 A-2	0.5055	10.1003		37.4367	0.3923	7839			83.20%	
SA 7-19 A-3	0.4968	10.0567		37.4159	0.3921	7938			84.25%	
SA 10-26 A-1	0.4976	10.1201		37.6737	0.3948	8030	7940	3.05%	85.23%	84.27%
SA 10-26 A-2	0.5080	10.1127		36.7730	0.3853	7666			81.36%	
SA 10-26 A-3	0.4809	10.1002		37.5689	0.3937	8125			86.23%	
SA 0-6 A-1	0.4940	15.1400	13118	30.9083	0.3227	9792	10075	3.21%	74.64%	76.80%
SA 0-6 A-2	0.4985	15.0053		31.8210	0.3324	10003			76.25%	
SA 0-6 A-3	0.5083	15.1767		33.1028	0.3459	10430			79.51%	
SA 4-13 A-1	0.5146	15.0656		34.7374	0.3632	10630	11021	3.08%	81.03%	84.01%
SA 4-13 A-2	0.4911	15.1141		34.9166	0.3650	11235			85.64%	
SA 4-13 A-3	0.5140	15.1230		36.3077	0.3806	11197			85.36%	
SA 7-20 A-1	0.5012	15.1839		34.7190	0.3630	10880	10279	6.25%	82.94%	78.36%
SA 7-20 A-2	0.5221	15.0782		34.1100	0.3567	10354			78.93%	
SA 7-20 A-3	0.4979	15.1020		30.3275	0.3166	9603			73.20%	
SA 10-27 A-1	0.5184	15.1230		34.6088	0.3618	10554	10501	0.74%	80.45%	80.74%
SA 10-27 A-2	0.5060	15.0712		33.4422	0.3600	10681			81.42%	
SA 10-27 A-3	0.5138	15.0849		34.3165	0.3587	10319			80.34%	

BO and MA: y = 94.707x + 0.3440   FF: y = 94.5266x + 0.4283

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FE Analyzed on 10/24/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
SA 0-7 A-1	0.5155	15.0109	14133	32.8172	0.3454	10003	10175	1.88%	70.77%	72.00%
SA 0-7 A-2	0.4956	15.0274		32.7200	0.3423	10380			73.45%	
SA 0-7 A-3	0.5265	15.0927		33.8056	0.3538	10141			71.77%	
SA 4-14 A-1	0.5104	15.0924		31.6970	0.3311	9621	9698	1.12%	68.07%	68.62%
SA 4-14 A-2	0.5122	15.0737		31.9091	0.3337	9822			69.50%	
SA 4-14 A-3	0.4935	15.1440		30.0940	0.3145	9651			68.29%	
SA 7-21 A-1	0.5144	15.1119		31.4225	0.3280	9650	9717	7.30%	68.30%	68.76%
SA 7-21 A-2	0.5004	15.1017		28.6912	0.2996	9042			63.98%	
SA 7-21 A-3	0.4928	15.0646		32.6949	0.3421	10457			73.99%	
SA 10-28 A-1	0.5035	15.0944		33.1499	0.3363	10081	9712	5.80%	71.33%	68.72%
SA 10-28 A-2	0.4988	15.1463		31.4624	0.3290	9990			70.69%	
SA 10-28 A-3	0.5003	15.0951		28.7629	0.3004	9063			64.13%	
BO and MA: $y = 94.7074x + 0.3440$ FE: $y = 94.3268x + 0.4283$										

NA = Not Applicable; ND = Not Detected

Cells shaded in light gray were re-analyzed on 11/16/2016 and 11/29/2016 due to low signal

Cells shaded in dark gray were re-analyzed on 12/05/2016 due to high %RSD.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation (SA MA Analyzed on 11/29/2016, SA FE Analyzed on 11/16/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/mL)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
SA 0-4 A-1	0.5148	10.0272	[illegible]	36.6329	0.3999	7710	7686	5.90%	88.16%	87.88%
SA 0-4 A-2	0.5072	10.1053		33.7418	0.3690	7222			82.58%	
SA 0-4 A-3	0.5260	10.0553		39.3638	0.4250	8124			92.90%	
SA 4-11 A-1	0.5160	10.0020		34.5090	0.3552	7249	7441	4.17%	82.89%	85.08%
SA 4-11 A-2	0.5120	10.0727		36.7481	0.3971	7798			89.16%	
SA 4-11 A-3	0.5188	9.9986		34.8752	0.3771	7275			83.18%	
SA 7-18 A-1	0.5093	10.0576		34.8911	0.3771	7450	7595	2.35%	85.21%	86.85%
SA 7-18 A-2	0.5045	10.0593		36.1730	0.3910	7793			89.13%	
SA 7-18 A-3	0.5119	10.0360		33.5720	0.3845	7539			86.20%	
SA 10-25 A-1	0.5229	9.9714		39.8556	0.4302	8204	7847	4.36%	93.80%	89.72%
SA 10-25 A-2	0.5085	9.9885		35.4250	0.3830	7523			86.02%	
SA 10-25 A-3	0.4999	10.0507		35.9512	0.3886	7817			89.33%	
SA 0-5 A-1	0.4950	10.1258	9422	38.6294	0.4407	9014	9034	0.27%	95.67%	95.88%
SA 0-5 A-2	0.5198	10.1349		40.6642	0.4630	9027			95.81%	
SA 0-5 A-3	0.5016	10.0224		39.7995	0.4535	9061			96.17%	
SA 4-12 A-1	0.5175	10.1298		39.8534	0.4541	8899	8918	1.60%	94.51%	94.65%
SA 4-12 A-2	0.4992	9.9998		39.7481	0.4529	9073			96.30%	
SA 4-12 A-3	0.5180	10.1190		38.4864	0.4301	8792			93.31%	
SA 7-19 A-1	0.5289	10.0654		40.2252	0.4582	8719	8720	1.44%	92.54%	92.61%
SA 7-19 A-2	0.5055	10.1001		37.7203	0.4307	8606			91.34%	
SA 7-19 A-3	0.4960	10.0567		38.3455	0.4376	8857			94.01%	
SA 10-26 A-1	0.4976	10.1203		38.4853	0.4390	8908	8836	1.57%	94.54%	93.78%
SA 10-26 A-2	0.5083	10.1127		36.2140	0.4161	8677			92.09%	
SA 10-26 A-3	0.4859	10.1092		37.8841	0.4325	8925			94.72%	
MA: y = 95.7869x - 0.4936 FE: y = 91.1622x - 1.5490										

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cont. (SA MA Analyzed on 11/29/2016, SA FE Analyzed on 11/16/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/mL)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
SA 0-6 A-1	0.5092	15.0268	13138	34.4515	0.3726	10996	11206	1.65%	83.82%	85.41%
SA 0-6 A-2	0.5009	15.1160		34.9543	0.3777	11285			85.92%	
SA 0-6 A-3	0.5181	15.1013		35.9998	0.3890	11339			86.44%	
SA 4-13 A-1	0.5010	15.0537		36.5576	0.3951	11887	12097	1.98%	90.62%	92.22%
SA 4-13 A-2	0.5029	15.0850		37.4660	0.4047	12141			92.55%	
SA 4-13 A-3	0.5181	15.1270		38.8934	0.4200	12262			93.48%	
SA 7-20 A-1	0.5012	15.1643		36.7517	0.3971	12032	12423	2.81%	91.72%	94.70%
SA 7-20 A-2	0.5129	15.2045		39.1280	0.4225	12524			95.47%	
SA 7-20 A-3	0.5024	15.1361		39.0795	0.4219	12712			96.91%	
SA 10-27 A-1	0.5102	15.1588		37.6042	0.4062	12069	12825	7.05%	92.01%	97.77%
SA 10-27 A-2	0.5016	15.1416		42.4640	0.4589	13826			105.40%	
SA 10-27 A-3	0.5031	15.1237		38.7567	0.4185	12581			95.90%	
SA 0-7 A-1	0.5155	15.0169	14133	36.3210	0.4153	12099	12808	4.86%	85.61%	90.62%
SA 0-7 A-2	0.4956	15.0274		38.3150	0.4374	13264			93.85%	
SA 0-7 A-3	0.5265	15.0927		39.9905	0.4556	13060			92.41%	
SA 4-14 A-1	0.5194	15.0924		40.0184	0.4561	13251	13191	1.98%	93.76%	93.33%
SA 4-14 A-2	0.5122	15.0737		40.0108	0.4559	13415			94.92%	
SA 4-14 A-3	0.4935	15.1440		36.7988	0.4205	12903			91.30%	
SA 7-21 A-1	0.5144	15.1119		40.2469	0.4584	13467	13547	5.94%	95.29%	95.85%
SA 7-21 A-2	0.5004	15.1011		37.0909	0.4237	12786			90.47%	
SA 7-21 A-3	0.4928	15.1646		41.3654	0.4707	14388			101.80%	
SA 10-28 A-1	0.5035	15.0944		40.7745	0.4642	13916	13762	4.70%	98.47%	97.38%
SA 10-28 A-2	0.4988	15.1463		41.4408	0.4715	14318			101.31%	
SA 10-28 A-3	0.5003	15.0951		37.8941	0.4326	13053			92.36%	
MA: y = 93.7869x - 0.4936 FE: y = 91.1622x + 5.100										

Cells shaded in gray were re-analyzed on 12/1/2016 due to low signal

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation (SA MA Analyzed on 12/01/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/mL)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
[illegible]	[illegible]	[illegible]	8746	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]			[illegible]	
[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]			[illegible]	
SA 4-11 A-1	0.5165	10.0020		37.2215	0.4109	7971	8238	4.35%	91.14%	94.19%
SA 4-11 A-2	0.5129	10.0027		39.9241	0.4402	8645			98.84%	
SA 4-11 A-3	0.5183	9.9986		38.0522	0.4190	8095			92.56%	
SA 7-18 A-1	0.5092	10.0576		37.0047	0.4084	8067	8200	2.41%	92.24%	93.76%
SA 7-18 A-2	0.5045	10.0591		38.3300	0.4227	8428			96.36%	
SA 7-18 A-3	0.5119	10.0360		37.4918	0.4135	8106			92.68%	
SA 10-25 A-1	0.5229	9.9713		41.8285	0.4611	8793	8453	4.09%	100.54%	96.65%
SA 10-25 A-2	0.5085	9.9885		37.4032	0.4125	8101			92.63%	
SA 10-25 A-3	0.4999	10.0307		38.1735	0.4210	8463			96.77%	
SA 0-6 A-1	0.5092	15.0268	13118	37.0226	0.4084	12031	12258	1.66%	91.87%	93.50%
SA 0-6 A-2	0.5060	15.1160		37.7147	0.4159	12425			94.71%	
SA 0-6 A-3	0.5181	15.1017		38.3277	0.4226	12319			93.91%	
y = 91.0251x - 0.1435										

Cells shaded in dark gray were re-analyzed on 12/05/2016 due to high %RSD.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 7 (Analyzed on 10/27/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
CV 1 A-1	0.5006	5.0092	0	ND	NA	NA	NA	NA	NA	NA
CV 1 A-2	0.5266	5.0722		ND	NA	NA			NA	
CV 1 A-3	0.5298	5.0778		ND	NA	NA			NA	
CV 2 A-1	0.5092	5.0349	6093	58.3544	0.6135	6066	6158	1.36%	99.56%	101.06%
CV 2 A-2	0.5008	5.0774		57.9590	0.6092	6177			101.37%	
CV 2 A-3	0.5195	5.0811		60.3476	0.6370	6211			102.26%	
CV 3 A-1	0.5299	10.0718	5824	27.6591	0.2838	5395	5326	1.85%	92.64%	91.45%
CV 3 A-2	0.5067	10.0522		25.6058	0.2628	5213			89.51%	
CV 3 A-3	0.503	10.0550		26.2448	0.2667	5371			92.22%	
CV 4 A-1	0.5057	5.0500	12318	106.3000	1.1505	11504	10861	7.20%	93.89%	88.17%
CV 4 A-2	0.5048	5.0435		94.1083	1.0028	10019			81.34%	
CV 4 A-3	0.5101	5.0590		104.5002	1.1011	11000			89.30%	
CV 5 A-1	0.5251	10.0494	11664	53.2493	0.5596	10691	10276	3.69%	91.66%	88.10%
CV 5 A-2	0.5192	10.0508		50.2725	0.5267	10186			87.33%	
CV 5 A-3	0.5029	10.0162		47.3505	0.4996	9951			85.31%	
CV 6 A-1	0.503	15.0725	18362	54.2243	0.5691	17055	16298	5.29%	92.85%	88.76%
CV 6 A-2	0.5215	14.7264		51.9149	0.5443	15371			83.71%	
CV 6 A-3	0.5344	15.0772		55.9118	0.5850	16464			89.09%	
CV 7 A-1	0.5134	15.0098	17567	46.0137	0.4810	14197	13655	3.48%	80.82%	77.73%
CV 7 A-2	0.5273	15.1902		44.2578	0.4621	13312			75.78%	
CV 7 A-3	0.5016	15.1660		43.6634	0.4550	13457			76.60%	
$y = 93.1257x + 1.2131$										

ND = Not Detected. NA = Not applicable.

Cells shaded in gray were re-analyzed on 10/31/2016 due to low signal.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 21 (Analyzed on 10/27/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
CV 8 A-1	0.5337	4.9359		ND	NA	NA			NA	
CV 8 A-2	0.5007	5.0720	0	ND	NA	NA	NA	NA	NA	NA
CV 8 A-3	0.529	5.0264		ND	NA	NA			NA	
CV 9 A-1	0.5046	5.0513		*	*	*			79.76%	
CV 9 A-2	0.5121	5.0661	7407	66.9236	0.7062	6987	6906	1.65%	94.33%	93.24%
CV 9 A-3	0.5022	5.0729		64.1538	0.6758	6826			92.16%	
CV 10 A-1	0.5272	5.0359		55.6407	0.5843	5582			94.21%	
CV 10 A-2	0.528	5.0816	5925	52.7617	0.5554	5329	5498	2.66%	89.95%	92.80%
CV 10 A-3	0.5046	5.0192		53.4989	0.5613	5584			94.24%	
CV 11 A-1	0.5067	10.0815		55.4971	0.5828	11282			76.61%	
CV 11 A-2	0.5157	10.0822	14727	50.2739	0.5289	10805	11082	2.24%	73.37%	75.25%
CV 11 A-3	0.5015	10.0588		53.0287	0.5563	11158			75.76%	
CV 12 A-1	0.5128	10.0763		51.5697	0.5408	10621			82.34%	
CV 12 A-2	0.5066	10.1009	12901	48.6799	0.5096	10120	10548	3.75%	78.45%	81.76%
CV 12 A-3	0.5043	10.0722		52.0458	0.5457	10900			84.49%	
CV 13 A-1	0.5023	15.1293		59.1599	0.6221	18691			85.73%	
CV 13 A-2	0.5046	15.1344	21943	57.0958	0.6000	17995	17078	4.66%	82.01%	81.93%
CV 13 A-3	0.5093	15.1557		54.8286	0.5756	17129			78.06%	
CV 14 A-1	0.515	15.2176		47.3566	0.4954	14639			75.92%	
CV 14 A-2	0.5141	15.1631	19281	48.8979	0.5119	15094	15091	2.97%	78.31%	78.27%
CV 14 A-3	0.5087	15.0909		49.9208	0.5218	15536			80.58%	

$y = 91.1257x + 1.2231$

ND – Not Detected. NA – Not applicable.

* Excluded due to non-trending result

Cells shaded in gray were re-analyzed on 10/31/2016 due to low signal.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Days 7 and 21 (Analyzed on 10/31/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
CV 4 A-1	0.5027	5.0500	12318	106.0878	1.1325	11384	12189	5.36%	92.41%	98.96%
CV 4 A-2	0.5048	5.0415		122.3369	1.2660	12672			102.87%	
CV 4 A-3	0.5101	5.0590		116.7180	1.2617	12513			101.58%	
CV 5 A-1	0.5251	10.0494	11664	59.1429	0.6219	11903	11408	3.90%	102.05%	97.81%
CV 5 A-2	0.5197	10.0928		55.5551	0.5934	11283			96.73%	
CV 5 A-3	0.5029	10.0362		52.8410	0.5540	11039			94.65%	
CV 6 A-1	0.503	15.0735	18362	63.6289	0.6701	20086	19400	4.21%	109.36%	105.31%
CV 6 A-2	0.5215	14.7264		61.7605	0.6500	18363			100.00%	
CV 6 A-3	0.5344	15.0972		66.4426	0.7003	19785			107.75%	
CV 7 A-1	0.5114	15.0958	17567	57.5589	0.6049	17857	17238	3.29%	97.29%	93.80%
CV 7 A-2	0.5273	15.1903		55.3460	0.5812	16742			91.18%	
CV 7 A-3	0.5016	15.1080		51.9331	0.5600	17116			93.21%	
CV 11 A-1	0.5167	10.0415	14727	63.8008	0.6720	13039	13093	4.16%	88.51%	88.91%
CV 11 A-2	0.5182	10.0272		62.5195	0.6583	12726			86.41%	
CV 11 A-3	0.5015	10.0599		64.1103	0.6753	13545			91.97%	
CV 12 A-1	0.5128	10.0707	12901	63.0154	0.6635	13038	12612	3.44%	101.06%	97.76%
CV 12 A-2	0.5066	10.1009		58.2956	0.6128	12171			94.34%	
CV 12 A-3	0.5043	10.0722		60.0914	0.6321	12625			97.86%	
CV 13 A-1	0.5023	15.1093	21940	67.1985	0.7085	21423	20796	3.11%	97.64%	94.73%
CV 13 A-2	0.5046	15.1344		65.8189	0.6936	20804			94.81%	
CV 13 A-3	0.5095	15.1557		64.2208	0.6765	20131			91.75%	
CV 14 A-1	0.515	15.2176	19281	59.1638	0.6222	18384	18829	2.66%	95.35%	97.65%
CV 14 A-2	0.5141	15.1631		60.5584	0.6350	18729			97.14%	
CV 14 A-3	0.507	15.0939		61.8215	0.6507	19372			100.47%	
$y = 93.1237x + 1.2237$										

Cells shaded in gray were re-analyzed on 12/05/2016 due to low signal.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Days 0, 7 and 21 (Analyzed on 12/05/2016)

Sample ID	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dose Level (ppm)	Peak Area	Calc. Conc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
CV 11 A-1	0.5292	10.0256	14727	69.2856	0.7601	14404	14292	2.61%	97.81%	97.05%
CV 11 A-2	0.5200	10.0164		66.2234	0.7245	13876			94.22%	
CV 11 A-3	0.5191	10.0179		69.1265	0.7504	14597			99.12%	
HO 4 A B-1	0.5035	5.1007	4573	47.3784	0.5180	5047	4873	6.87%	119.92%	101.43%
HO 4 A B-2	0.5161	5.1545		42.1655	0.4608	4602			105.24%	
HO 4 A B-3	0.5101	5.1601		43.1390	0.4715	4769			109.08%	
CV 9 A-1	0.5014	5.1682	7407	60.8553	0.6657	6862	7421	7.05%	92.64%	100.19%
CV 9 A-2	0.5054	5.1490		67.3114	0.7365	7504			101.31%	
CV 9 A-3	0.5068	5.1540		70.9612	0.7769	7898			106.63%	
HO 10 A B-1	0.5221	10.0158	8746	41.1590	0.4498	8628	8250	4.06%	98.65%	94.33%
HO 10 A B-2	0.5057	10.0045		36.9784	0.4040	7992			91.37%	
HO 10 A B-3	0.5001	9.9898		37.8552	0.4136	8131			92.97%	
HO 14 A T-1	0.5159	15.1945	13118	38.9261	0.4217	12419	12226	3.70%	94.67%	93.20%
HO 14 A T-2	0.5051	15.1446		38.3451	0.4189	12561			95.79%	
HO 14 A T-3	0.5083	15.2688		35.6651	0.3895	11697			89.17%	
SA 0-2 A-1	0.5212	5.1675	4373	42.3967	0.4632	4593	4508	5.06%	105.03%	103.08%
SA 0-2 A-2	0.5251	5.1092		41.9033	0.4580	4725			108.05%	
SA 0-2 A-3	0.5184	5.1511		38.7419	0.4233	4206			96.18%	
SA 10-27 A-1	0.5925	15.2280	13118	36.7208	0.4011	11471	10559	7.49%	87.45%	80.49%
SA 10-27 A-2	0.5217	15.3743		31.8556	0.3478	10116			77.11%	
SA 10-27 A-3	0.5304	15.2121		32.3808	0.3537	10086			76.91%	
SA 0-4 A-1	0.5233	9.9558	8746	38.0874	0.4162	7918	7951	0.57%	90.53%	90.91%
SA 0-4 A-2	0.5322	10.0217		38.8961	0.4250	8002			91.50%	
SA 0-4 A-3	0.5051	10.0204		36.5978	0.3998	7931			90.68%	
$y = 91.2192x - 0.1319$										

Cells shaded in gray were excluded from analysis due to high %RSD. Original data was used in analysis.

APPENDIX E: OPHTHALMOLOGY

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

Kristina R. Vygantas, DVM, Diplomate American College of Veterinary Ophthalmologists
319 Perrineville Rd.
Robbinsville, NJ 08691
609.259.8300 (work)

Exam Date: September 23, 2016

Eurofins Study No: ~~160720-5R~~ 43166 (b) 11/15/16
PSL No. 160720-5R

44 male and 44 female SD rats were examined. The examination was performed under dim light conditions after pharmacologic mydriasis with 1% tropicamide ophthalmic solution. Both eyes of each animal were examined using slit lamp biomicroscopy and indirect ophthalmoscopy. All animals were all normal on ophthalmic exam and thus, suitable for inclusion in this study.

(b) (6)

Kristina R. Vygantas, DVM
Diplomate, American College of Veterinary Ophthalmologists

Kristina R. Vygantas, DVM, Diplomate American College of Veterinary Ophthalmologists
319 Perrineville Rd.
Robbinsville, NJ 08691
609.259.8300 (work)

Exam Date: October 21, 2016

Eurofins Study No: 43166
PSL No. 160720-5R

40 male and 40 female SD rats were examined. The examination was performed under dim light conditions after pharmacologic mydriasis with 1% tropicamide ophthalmic solution. Both eyes of each animal were examined using slit lamp biomicroscopy and indirect ophthalmoscopy. All animals were all normal on ophthalmic exam, thus the test substance was not considered an ocular toxicant.

(b) (6) [redacted]

Kristina R. Vygantas, DVM
Diplomate, American College of Veterinary Ophthalmologists

APPENDIX F: INDIVIDUAL ANIMAL IN-LIFE CLINICAL OBSERVATIONS[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	m	7001	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7002	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7003	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7004	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7005	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7006	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7007	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7008	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7009	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7010	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	20	21	22	23	24	25	26	27	28	29	30
1	m	7001	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7002	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7003	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7004	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7005	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7006	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7007	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7008	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7009	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7010	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
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Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
2	m	7021	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7022	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7023	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7024	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7025	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7026	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7027	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7028	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7029	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7030	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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2	m	7021	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7022	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7023	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7024	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7025	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7026	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7027	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7028	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7029	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7030	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.

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A 28-Day Dietary Study in Rats

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Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
3	m	7041	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7042	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7043	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7044	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7045	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7046	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7047	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7048	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7049	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7050	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Individual Animal Clinical Observations

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A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	20	21	22	23	24	25	26	27	28	29	30
3	m	7041	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7042	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7043	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7044	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7045	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7046	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7047	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7048	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7049	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7050	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.

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Individual Animal Clinical Observations

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Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
4	m	7061	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.
		7062	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7063	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7064	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7065	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.
		7066	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.
		7067	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.
		7068	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.
		7069	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.
			Eschar	Head	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		7070	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.

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Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	20	21	22	23	24	25	26	27	28	29	30
4	m	7061	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.
		7062	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7063	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7064	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
		7065	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.
		7066	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.
		7067	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.
		7068	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.
		7069	No Abnormalities Detected		X	X	X	X	X	X	X	X	.	.	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.
			Eschar	Head	.	.	.	.	.	.	.	.	F	F	.
		7070	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.
			Staining	Cage Pan	.	.	.	.	.	.	.	.	.	.	.

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Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	f	7011	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7012	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7013	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7014	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7015	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7016	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7017	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7018	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7019	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7020	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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1	f	7011	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7012	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7013	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7014	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7015	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7016	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7017	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7018	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7019	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7020	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X

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2	f	7031	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7032	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7033	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7034	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7035	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Alopecia	Left Forelimb	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Alopecia	Right Forelimb	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		7036	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7037	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7038	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7039	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7040	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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2	f	7031	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7032	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7033	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7034	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7035	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.	.
			Alopecia	Left Forelimb	.	S	S	S	S	S	S	S	M	M	M
			Alopecia	Right Forelimb	.	S	S	S	S	S	S	S	M	M	M
		7036	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7037	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7038	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7039	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7040	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

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Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
3	f	7051	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7052	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7053	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7054	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7055	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7056	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7057	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7058	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7059	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7060	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	20	21	22	23	24	25	26	27	28	29	30
3	f	7051	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7052	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7053	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7054	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7055	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7056	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7057	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7058	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7059	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7060	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
4	f	7071	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7072	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7073	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7074	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7075	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7076	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7077	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7078	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7079	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		7080	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	20	21	22	23	24	25	26	27	28	29	30
4	f	7071	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7072	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7073	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7074	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7075	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7076	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7077	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7078	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7079	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		7080	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

APPENDIX G: DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

APPENDIX G: DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

Removal from Cage and Open Field Observations	
Activity/Arousal	0. Alternating behaviors - animal goes through normal repertoire of behaviors during observation period. These consist of exploring, sniffing, grooming, rearing, etc. 1. Inactive/Alert - animal sits in one place during the observation period but appears to be aware of its surroundings. It may go through its normal repertoire of activities but the majority of the observation period is spent not moving. 2. Hypoactive/Not alert - animal sits in one place during the observation period. Animal appears to be unaware of its surroundings or in a stupor. 3. Hyperactive/Hyperalert - animal appears excited. Animal may dart and freeze during the observation period or animal may sit in one place and jump at any sound or movement.
Biting	0. None 1. Biting cage 2. Self-mutilation
Circling	0. Absent 1. Present
Convulsions	0. None 1. Clonic – alternating periods of contraction and relaxation of muscles 2. Tonic – prolonged period of muscle contractions
Defecation	0. None/Normal 1. Soft (partially formed) 2. Diarrhea (watery feces)
Ease of Removal/Handling	0. Slight/moderate resistance - animal is easy to handle, may squirm or vocalize occasionally. 1. No resistance - animal is limp/flaccid when being handled. 2. High resistance/aggressive - animal is difficult to handle, and/or squirms continuously, and/or tries to bite handler. 3. Aggressive - biting or lunging behavior specifically directed at handler.
Emaciation	0. Absent 1. Present (confirmed using body weights)
Eyes	0. Normal 1. Exophthalmos - abnormal protrusion of eyeball 2. Endophthalmus – sunken eyeball 3. Eye damaged – mechanical damage (e.g. orbital bleeding, etc.)
Fur/Skin Appearance	0. Normal 1. Unkempt - coat rough or ungroomed, may be slightly stained 2. Urine stained/wetness (Ano-genital staining) 3. Hair loss
Gait	0. Normal 1. Abnormal – limbs exaggerated/splayed, hind limbs and/or forelimbs show exaggerated placement or movement 2. Non weight bearing (Limping)
Lacrimation	0. Absent 1. Present - lacrimation noticeable. 2. Excessive - animal has excessive amount of tearing. Note: Descriptors (i.e. color of ocular discharge will be noted on daily observation sheet).
Locomotion	0. Normal 1. Somewhat impaired 2. Totally impaired

APPENDIX G (cont.): DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

Mucous Membranes	0. Normal 1. Present – mucous noticeable 2. Excessive – animal has an excessive amount of mucous present
Muscle Tone	0. Normal - muscles are resilient and firm and the hind legs go through their full range of motion. 1. Increased - muscles are rigid, hind limbs will not go through their full range of motion. 2. Decreased - muscles are flaccid, hind limbs have little or no resistance to movement
Palpebral Closure	0. Eyes wide open 1. Eyes halfway shut 2. Eyes completely shut
Piloerection	0. Absent 1. Present
Posture	0. Normal (awake) – alert, sitting, standing, or rearing 1. Normal (sleeping) – curled up, usually with head down 2. Hunched – abnormal posture 3. Flattened (prone) – limbs spread out lying flat or on one side
Respiratory Pattern	0. Normal 1. Slow 2. Rapid 3. Rales (Moist or Dry) 4. Gasping 5. Labored - Dyspnea
Salivation	0. None 1. Present - salivation is noticeable around the edge of the mouth 2. Excessive - salivation extends to the fur around the jaw
Tremors	0. None 1. Slight – localized to one area, or a twitch/spasm of a localized area 2. Severe – more than one area or involving whole body 3. Fasciculation – wave-like ripples of a muscle or group of muscles
Unusual Behaviors	0. Absent 1. Present – Be specific in describing all unusual behaviors on data sheet.
Urination	0. None/Normal 1. Excessive
Vocalization, removal from cage	0. Absent 1. Present - animal vocalizes unprovoked or continuously vocalizes when being handled.
Vocalizations, open field observations	0. Absent 1. Present
Writhing	0. Absent 1. Present
Manipulative Tests	
Pupillary reflex	0. Normal 1. Slow or absent- pupil reaction is slow or absent.

APPENDIX H: INDIVIDUAL ANIMAL DETAILED CLINICAL OBSERVATIONS[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7010	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7001	0	0	0
7002	0	0	0
7003	0	0	0
7004	0	0	0
7005	0	0	0
7006	0	0	0
7007	0	0	0
7008	0	0	0
7009	0	0	0
7010	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7030	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7021	0	0	0
7022	0	0	0
7023	0	0	0
7024	0	0	0
7025	0	0	0
7026	0	0	0
7027	0	0	0
7028	0	0	0
7029	0	0	0
7030	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7044	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7045	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7046	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7047	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7048	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7049	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7050	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7041	0	0	0
7042	0	0	0
7043	0	0	0
7044	0	0	0
7045	0	0	0
7046	0	0	0
7047	0	0	0
7048	0	0	0
7049	0	0	0
7050	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7061	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7062	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7063	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7064	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7065	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7066	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7067	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7068	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7069	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7070	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7061	0	0	0
7062	0	0	0
7063	0	0	0
7064	0	0	0
7065	0	0	0
7066	0	0	0
7067	0	0	0
7068	0	0	0
7069	0	0	0
7070	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7020	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7011	0	0	0
7012	0	0	0
7013	0	0	0
7014	0	0	0
7015	0	0	0
7016	0	0	0
7017	0	0	0
7018	0	0	0
7019	0	0	0
7020	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	3	3	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43168
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7037	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7038	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7040	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7031	0	0	0
7032	0	0	0
7033	0	0	0
7034	0	0	0
7035	0	0	0
7036	0	0	0
7037	0	0	0
7038	0	0	0
7039	0	0	0
7040	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7051	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7058	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7059	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7051	0	0	0
7052	0	0	0
7053	0	0	0
7054	0	0	0
7055	0	0	0
7056	0	0	0
7057	0	0	0
7058	0	0	0
7059	0	0	0
7060	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral Closure	Palpebral Closure	Palpebral Closure	Palpebral Closure
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Palpebral Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Lacrimation	Eye	Eye	Eye	Eye	Eye	Mucous Membranes	Mucous Membranes	Mucous Membranes
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Emaciation	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)													
	Piloerection	Piloerection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	14	21	28	0	7	14	21	28	0	7	14	21	28	0
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Removal from Cage)									DetClinObs (Open Field Obs)				
	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	14	21	28	0	7	14	21	28
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)													
	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Tremors	Tremors	Tremors	Tremors	Tremors	Posture	Posture	Posture	Posture
	0	7	14	21	28	0	7	14	21	28	0	7	14	21
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 1	DetClinObs (Open Field Obs)													
	Posture	Gait	Gait	Gait	Gait	Gait	Locomotion	Locomotion	Locomotion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	28	0	7	14	21	28	0	7	14	21	28	0	7	14
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)													
	Defecation	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7071	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7072	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7073	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7078	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7080	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	DetClinObs (Open Field Obs)		
	Vocalization (OF)	Vocalization (OF)	Vocalization (OF)
	14	21	28
7071	0	0	0
7072	0	0	0
7073	0	0	0
7074	0	0	0
7075	0	0	0
7076	0	0	0
7077	0	0	0
7078	0	0	0
7079	0	0	0
7080	0	0	0

APPENDIX I: INDIVIDUAL ANIMAL BODY WEIGHTS[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

0 mg/kg/day Group 1	Day(s) Relative to Start Date				
	0	7	14	21	28
7001	240	297	345	396	429
7002	232	273	327	362	382
7003	238	288	334	379	401
7004	234	271	310	343	360
7005	228	267	305	340	357
7006	247	303	347	404	434
7007	242	308	358	400	430
7008	230	283	328	361	379
7009	241	297	342	381	400
7010	232	290	327	366	375
Mean	236.4	287.7	332.3	373.2	394.7
SD	6.1	14.0	16.5	22.7	28.8
N	10	10	10	10	10

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

512 mg/kg/day Group 2	Day(s) Relative to Start Date				
	0	7	14	21	28
7021	232	284	324	363	390
7022	236	295	346	383	403
7023	243	299	353	392	415
7024	246	298	346	383	400
7025	237	291	331	369	387
7026	232	288	345	381	403
7027	240	291	330	374	398
7028	228	273	309	341	355
7029	241	306	370	421	458
7030	229	271	316	359	380
Mean	236.4	289.6	337.0	376.6	398.9
SD	6.1	11.1	18.4	21.4	26.4
N	10	10	10	10	10

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date				
	0	7	14	21	28
7041	238	281	333	377	402
7042	250	306	367	419	448
7043	232	282	322	366	382
7044	231	295	353	401	434
7045	233	288	337	378	401
7046	244	308	371	415	448
7047	239	304	360	406	433
7048	241	303	360	411	445
7049	232	270	309	337	364
7050	227	272	304	335	345
Mean	236.7	290.9	341.6	384.5	410.2
SD	7.0	14.3	24.2	31.1	37.2
N	10	10	10	10	10

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date				
	0	7	14	21	28
7061	241	295	342	380	404
7062	234	288	335	374	403
7063	233	270	305	345	369
7064	240	304	363	418	446
7065	246	308	362	404	432
7066	239	299	351	396	421
7067	244	306	355	394	420
7068	226	281	326	362	385
7069	229	293	326	360	379
7070	231	284	330	366	396
Mean	236.3	292.8	339.5	379.9	405.5
SD	6.7	12.2	18.6	22.7	24.4
N	10	10	10	10	10

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

0 mg/kg/day Group 1	Day(s) Relative to Start Date				
	0	7	14	21	28
7011	165	178	188	204	208
7012	163	188	204	223	228
7013	197	210	261	282	288
7014	187	222	220 [1]	249	253
7015	181	205	217	243	252
7016	169	195	212	225	250
7017	156	176	192	209	223
7018	175	201	224	255	262
7019	180	212	239	244	264
7020	168	196	231	258	270
Mean	174.1	198.3	218.8	239.2	249.8
SD	12.3	14.8	21.9	24.0	24.0
N	10	10	10	10	10

1 [RC:Reweighed, food and water OK]

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

512 mg/kg/day Group 2	Day(s) Relative to Start Date				
	0	7	14	21	28
7031	192	217	239	246	257
7032	175	195	208	224	237
7033	173	200	210	228 [1]	238
7034	162	183	198	208	219
7035	168	194	218	229	244
7036	168	202	218	233	249
7037	153	169	182	187	196
7038	193	220	236	250	265
7039	183	215	241	240 [2]	260
7040	177	215	235	246	275
Mean	174.4	201.0	218.5	229.1	244.0
SD	12.6	16.5	19.6	19.4	23.3
N	10	10	10	10	10

1 [. RC:Reweighed, food and water OK]

2 [RC:Reweighed, food and water OK]

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date				
	0	7	14	21	28
7051	162	189	202	210	229
7052	162	192	216	224	238
7053	182	210	231	249	267
7054	189	216	239	255	267
7055	198	224	236	268	277
7056	176	214	239	257	266
7057	166	185	204	221	237
7058	169	198	215	228	237
7059	180	214	238	251	270
7060	172	198	217	225	244
Mean	175.6	204.0	223.7	238.8	253.2
SD	11.8	13.3	14.6	19.4	17.7
N	10	10	10	10	10

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Bodyweight (g)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date				
	0	7	14	21	28
7071	171	198	212	240	248
7072	168	196	218	229	246
7073	181	208	232	244	263
7074	179	195	215	229	234
7075	177	201	218	229	241
7076	163	190	219	242	245
7077	187	215	241	260	271
7078	162	191	213	224	237
7079	196	215	246	258	262
7080	159	184	199	225	240
Mean	174.3	199.3	221.3	238.0	248.7
SD	11.9	10.5	14.3	13.1	12.4
N	10	10	10	10	10

APPENDIX J: INDIVIDUAL ANIMAL MEAN DAILY BODY WEIGHT GAIN[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Mean Daily Body Weight Gain (g/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7001	8.1	6.9	7.3	4.7	6.8
7002	5.9	7.7	5.0	2.9	5.4
7003	7.1	6.6	6.4	3.1	5.8
7004	5.3	5.6	4.7	2.4	4.5
7005	5.6	5.4	5.0	2.4	4.6
7006	8.0	6.3	8.1	4.3	6.7
7007	9.4	7.1	6.0	4.3	6.7
7008	7.6	6.4	4.7	2.6	5.3
7009	8.0	6.4	5.6	2.7	5.7
7010	8.3	5.3	5.6	1.3	5.1
Mean	7.33	6.37	5.84	3.07	5.65
SD	1.35	0.77	1.15	1.06	0.84
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

512 mg/kg/day Group 2	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7021	7.4	5.7	5.6	3.9	5.6
7022	8.4	7.3	5.3	2.9	6.0
7023	8.0	7.7	5.6	3.3	6.1
7024	7.4	6.9	5.3	2.4	5.5
7025	7.7	5.7	5.4	2.6	5.4
7026	8.0	8.1	5.1	3.1	6.1
7027	7.3	5.6	6.3	3.4	5.6
7028	6.4	5.1	4.6	2.0	4.5
7029	9.3	9.1	7.3	5.3	7.8
7030	6.0	6.4	6.1	3.0	5.4
Mean	7.60	6.77	5.66	3.19	5.80
SD	0.94	1.30	0.75	0.91	0.83
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Mean Daily Body Weight Gain (g/day)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7041	6.1	7.4	6.3	3.6	5.9
7042	8.0	8.7	7.4	4.1	7.1
7043	7.1	5.7	6.3	2.3	5.4
7044	9.1	8.3	6.9	4.7	7.3
7045	7.9	7.0	5.9	3.3	6.0
7046	9.1	9.0	6.3	4.7	7.3
7047	9.3	8.0	6.6	3.9	6.9
7048	8.9	8.1	7.3	4.9	7.3
7049	5.4	5.6	4.0	3.9	4.7
7050	6.4	4.6	4.4	1.4	4.2
Mean	7.74	7.24	6.13	3.67	6.20
SD	1.40	1.49	1.12	1.10	1.14
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7061	7.7	6.7	5.4	3.4	5.8
7062	7.7	6.7	5.6	4.1	6.0
7063	5.3	5.0	5.7	3.4	4.9
7064	9.1	8.4	7.9	4.0	7.4
7065	8.9	7.7	6.0	4.0	6.6
7066	8.6	7.4	6.4	3.6	6.5
7067	8.9	7.0	5.6	3.7	6.3
7068	7.9	6.4	5.1	3.3	5.7
7069	9.1	4.7	4.9	2.7	5.4
7070	7.6	6.6	5.1	4.3	5.9
Mean	8.07	6.67	5.77	3.66	6.04
SD	1.16	1.13	0.86	0.47	0.70
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7011	1.9	1.4	2.3	0.6	1.5
7012	3.6	2.3	2.7	0.7	2.3
7013	1.9	7.3	3.0	0.9	3.3
7014	5.0	-0.3	4.1	0.6	2.4
7015	3.4	1.7	3.7	1.3	2.5
7016	3.7	2.4	1.9	3.6	2.9
7017	2.9	2.3	2.4	2.0	2.4
7018	3.7	3.3	4.4	1.0	3.1
7019	4.6	3.9	0.7	2.9	3.0
7020	4.0	5.0	3.9	1.7	3.6
Mean	3.46	2.93	2.91	1.51	2.70
SD	1.03	2.09	1.15	1.03	0.60
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Mean Daily Body Weight Gain (g/day)

512 mg/kg/day Group 2	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7031	3.6	3.1	1.0	1.6	2.3
7032	2.9	1.9	2.3	1.9	2.2
7033	3.9	1.4	2.6	1.4	2.3
7034	3.0	2.1	1.4	1.6	2.0
7035	3.7	3.4	1.6	2.1	2.7
7036	4.9	2.3	2.1	2.3	2.9
7037	2.3	1.9	0.7	1.3	1.5
7038	3.9	2.3	2.0	2.1	2.6
7039	4.6	3.7	-0.1	2.9	2.8
7040	5.4	2.9	1.6	4.1	3.5
Mean	3.80	2.50	1.51	2.13	2.49
SD	0.96	0.75	0.82	0.85	0.53
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7051	3.9	1.9	1.1	2.7	2.4
7052	4.3	3.4	1.1	2.0	2.7
7053	4.0	3.0	2.6	2.6	3.0
7054	3.9	3.3	2.3	1.7	2.8
7055	3.7	1.7	4.6	1.3	2.8
7056	5.4	3.6	2.6	1.3	3.2
7057	2.7	2.7	2.4	2.3	2.5
7058	4.1	2.4	1.9	1.3	2.4
7059	4.9	3.4	1.9	2.7	3.2
7060	3.7	2.7	1.1	2.7	2.6
Mean	4.06	2.81	2.16	2.06	2.77
SD	0.72	0.66	1.03	0.63	0.30
N	10	10	10	10	10

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7071	3.9	2.0	4.0	1.1	2.8
7072	4.0	3.1	1.6	2.4	2.8
7073	3.9	3.4	1.7	2.7	2.9
7074	2.3	2.9	2.0	0.7	2.0
7075	3.4	2.4	1.6	1.7	2.3
7076	3.9	4.1	3.3	0.4	2.9
7077	4.0	3.7	2.7	1.6	3.0
7078	4.1	3.1	1.6	1.9	2.7
7079	2.7	4.4	1.7	0.6	2.4
7080	3.6	2.1	3.7	2.1	2.9
Mean	3.57	3.14	2.39	1.53	2.66
SD	0.61	0.81	0.96	0.79	0.34
N	10	10	10	10	10

APPENDIX K: INDIVIDUAL ANIMAL MEAN DAILY FOOD CONSUMPTION[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7001	28.0	27.3	27.0	27.3	27.9	22.3	29.3	27.2
7002	28.0	27.3	27.0	27.3	27.9	22.3	29.3	27.2
7003	27.0	24.5	26.3	24.8	25.1	20.8	26.5	25.2
7004	27.0	24.5	26.3	24.8	25.1	20.8	26.5	25.2
7005	28.1	25.2	24.6	25.3	25.9	21.8	27.6	25.7
7006	28.1	25.2	24.6	25.3	25.9	21.8	27.6	25.7
7007	29.9	27.7	28.0	26.0	26.8	22.8	28.3	27.2
7008	29.9	27.7	28.0	26.0	26.8	22.8	28.3	27.2
7009	27.1	26.8	26.9	26.0	26.3	21.2	26.9	26.0
7010	27.1	26.8	26.9	26.0	26.3	21.2	26.9	26.0
Mean	28.03	26.30	26.55	25.90	26.38	21.80	27.70	26.26
SD	1.08	1.31	1.17	0.89	0.97	0.77	1.04	0.86
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

512 mg/kg/day Group 2	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7021	28.8	26.2	26.9	25.2	25.9	21.5	27.6	26.2
7022	28.8	26.2	26.9	25.2	25.9	21.5	27.6	26.2
7023	29.4	27.5	27.6	25.0	26.4	21.5	27.5	26.6
7024	29.4	27.5	27.6	25.0	26.4	21.5	27.5	26.6
7025	28.8	27.8	27.4	24.0	26.5	21.8	29.3	26.7
7026	28.8	27.8	27.4	24.0	26.5	21.8	29.3	26.7
7027	28.1	26.2	25.9	24.3	25.9	21.5	28.8	26.0
7028	28.1	26.2	25.9	24.3	25.9	21.5	28.8	26.0
7029	28.0	27.8	28.5	28.8	27.9	24.0	30.6	28.1
7030	28.0	27.8	28.5	28.8	27.9	24.0	30.6	28.1
Mean	28.60	27.10	27.25	25.47	26.50	22.07	28.75	26.73
SD	0.52	0.81	0.91	1.83	0.77	1.03	1.21	0.76
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7041	28.3	29.0	29.5	29.5	29.3	23.0	30.6	28.6
7042	28.3	29.0	29.5	29.5	29.3	23.0	30.6	28.6
7043	29.8	27.8	27.6	27.8	27.1	22.0	28.4	27.4
7044	29.8	27.8	27.6	27.8	27.1	22.0	28.4	27.4
7045	30.0	29.0	29.8	25.2	27.5	24.3	30.3	28.2
7046	30.0	29.0	29.8	25.2	27.5	24.3	30.3	28.2
7047	28.6	29.0	28.6	27.2	28.6	22.3	30.5	28.0
7048	28.6	29.0	28.6	27.2	28.6	22.3	30.5	28.0
7049	24.5	24.2	23.9	22.0	23.0	19.7	25.9	23.5
7050	24.5	24.2	23.9	22.0	23.0	19.7	25.9	23.5
Mean	28.23	27.80	27.88	26.33	27.10	22.27	29.13	27.14
SD	2.08	1.97	2.25	2.71	2.31	1.61	1.92	1.98
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7061	27.8	27.7	26.8	26.2	25.6	21.3	28.1	26.3
7062	27.8	27.7	26.8	26.2	25.6	21.3	28.1	26.3
7063	28.5	27.7	26.4	25.3	27.5	23.2	27.5	26.7
7064	28.5	27.7	26.4	25.3	27.5	23.2	27.5	26.7
7065	29.4	27.7	28.6	26.7	27.9	22.8	30.1	27.8
7066	29.4	27.7	28.6	26.7	27.9	22.8	30.1	27.8
7067	30.1	29.3	28.6	27.3	27.3	22.7	30.8	28.2
7068	30.1	29.3	28.6	27.3	27.3	22.7	30.8	28.2
7069	27.4	27.2	26.9	25.3	26.4	22.3	29.4	26.6
7070	27.4	27.2	26.9	25.3	26.4	22.3	29.4	26.6
Mean	28.63	27.90	27.45	26.17	26.93	22.47	29.18	27.13
SD	1.07	0.78	1.03	0.82	0.86	0.66	1.28	0.78
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (g/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7011	19.9	17.3	17.8	18.0	17.4	14.8	18.4	17.8
7012	19.9	17.3	17.8	18.0	17.4	14.8	18.4	17.8
7013	22.4	23.2	21.6	21.7	22.3	16.2	21.3	21.3
7014	22.4	23.2	21.6	21.7	22.3	16.2	21.3	21.3
7015	22.1	18.3	19.0	18.7	19.6	16.5	21.3	19.5
7016	22.1	18.3	19.0	18.7	19.6	16.5	21.3	19.5
7017	21.9	17.8	18.4	18.7	19.3	15.3	20.4	19.0
7018	21.9	17.8	18.4	18.7	19.3	15.3	20.4	19.0
7019	19.6	20.0	21.0	19.3	20.9	16.7	22.3	20.1
7020	19.6	20.0	21.0	19.3	20.9	16.7	22.3	20.1
Mean	21.18	19.33	19.55	19.27	19.88	15.90	20.70	19.55
SD	1.24	2.23	1.59	1.34	1.72	0.74	1.38	1.24
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Mean Daily Food Consumption (g/day)

512 mg/kg/day Group 2	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7031	22.1	19.0	23.8	20.5	19.9	16.2	23.5	21.0
7032	22.1	19.0	23.8	20.5	19.9	16.2	23.5	21.0
7033	20.3	18.2	18.3	20.0	19.0	15.3	20.9	19.0
7034	20.3	18.2	18.3	20.0	19.0	15.3	20.9	19.0
7035	20.3	18.3	18.9	18.7	19.0	16.0	20.1	18.9
7036	20.3	18.3	18.9	18.7	19.0	16.0	20.1	18.9
7037	22.9	17.7	20.6	18.8	22.0	16.3	19.9	20.0
7038	22.9	17.7	20.6	18.8	22.0	16.3	19.9	20.0
7039	20.6	19.0	20.8	19.0	20.5	17.3	22.3	20.1
7040	20.6	19.0	20.8	19.0	20.5	17.3	22.3	20.1
Mean	21.23	18.43	20.45	19.40	20.08	16.23	21.33	19.78
SD	1.13	0.54	2.02	0.76	1.18	0.68	1.44	0.82
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Mean Daily Food Consumption (g/day)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7051	20.9	17.5	18.4	17.7	17.3	15.8	20.5	18.4
7052	20.9	17.5	18.4	17.7	17.3	15.8	20.5	18.4
7053	22.0	19.7	20.6	19.5	20.8	15.5	22.3	20.3
7054	22.0	19.7	20.6	19.5	20.8	15.5	22.3	20.3
7055	22.9	23.2	20.4	20.0	20.6	16.3	21.4	20.8
7056	22.9	23.2	20.4	20.0	20.6	16.3	21.4	20.8
7057	19.9	17.2	18.0	16.8	18.0	15.8	19.8	18.1
7058	19.9	17.2	18.0	16.8	18.0	15.8	19.8	18.1
7059	19.6	19.0	19.9	18.3	20.1	16.3	21.5	19.4
7060	19.6	19.0	19.9	18.3	20.1	16.3	21.5	19.4
Mean	21.05	19.30	19.45	18.47	19.35	15.97	21.08	19.40
SD	1.31	2.26	1.12	1.22	1.52	0.34	0.91	1.09
N	10	10	10	10	10	10	10	10

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (g/day)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date							
	3 → 7	7 → 10	10 → 14	14 → 17	17 → 21	21 → 24	24 → 28	3 → 28
7071	19.8	17.2	17.0	17.8	18.1	14.7	20.8	18.1
7072	19.8	17.2	17.0	17.8	18.1	14.7	20.8	18.1
7073	21.1	19.2	19.6	17.0	19.9	16.2	19.6	19.1
7074	21.1	19.2	19.6	17.0	19.9	16.2	19.6	19.1
7075	20.5	19.3	19.5	19.5	19.0	16.0	21.1	19.4
7076	20.5	19.3	19.5	19.5	19.0	16.0	21.1	19.4
7077	20.5	19.8	19.4	19.7	19.6	15.7	20.1	19.4
7078	20.5	19.8	19.4	19.7	19.6	15.7	20.1	19.4
7079	19.0	19.0	19.9	19.7	19.0	15.7	20.6	19.1
7080	19.0	19.0	19.9	19.7	19.0	15.7	20.6	19.1
Mean	20.18	18.90	19.08	18.73	19.13	15.63	20.45	19.00
SD	0.77	0.96	1.11	1.17	0.64	0.55	0.55	0.52
N	10	10	10	10	10	10	10	10

APPENDIX L: INDIVIDUAL ANIMAL FOOD EFFICIENCY[1,2]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Food efficiency = $\frac{\text{Mean Daily Body Weight Gain}}{\text{Mean Daily Food Consumption}}$

[2] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

0 mg/kg/day Group 1	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7001	0.36	0.25	0.26	0.18
7002	0.26	0.28	0.18	0.11
7003	0.32	0.26	0.26	0.13
7004	0.24	0.22	0.19	0.10
7005	0.24	0.22	0.19	0.10
7006	0.34	0.25	0.32	0.17
7007	0.36	0.26	0.23	0.17
7008	0.29	0.23	0.18	0.10
7009	0.31	0.24	0.21	0.11
7010	0.32	0.20	0.21	0.05
Mean	0.304	0.241	0.223	0.121
SD	0.046	0.025	0.044	0.040
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Food Efficiency

512 mg/kg/day Group 2	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7021	0.31	0.22	0.22	0.15
7022	0.35	0.27	0.21	0.11
7023	0.33	0.28	0.22	0.13
7024	0.31	0.25	0.20	0.10
7025	0.32	0.21	0.21	0.10
7026	0.33	0.30	0.20	0.12
7027	0.30	0.21	0.25	0.13
7028	0.27	0.20	0.18	0.08
7029	0.36	0.32	0.26	0.19
7030	0.23	0.23	0.22	0.11
Mean	0.312	0.248	0.217	0.123
SD	0.038	0.043	0.022	0.032
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

1024 mg/kg/day Group 3	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7041	0.27	0.25	0.21	0.13
7042	0.35	0.30	0.25	0.15
7043	0.30	0.21	0.23	0.09
7044	0.38	0.30	0.25	0.18
7045	0.31	0.24	0.22	0.12
7046	0.37	0.31	0.24	0.17
7047	0.37	0.28	0.23	0.14
7048	0.35	0.28	0.26	0.18
7049	0.23	0.23	0.18	0.17
7050	0.27	0.19	0.20	0.06
Mean	0.319	0.258	0.227	0.139
SD	0.051	0.041	0.026	0.040
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

1536 mg/kg/day Group 4	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7061	0.34	0.25	0.21	0.14
7062	0.34	0.25	0.22	0.16
7063	0.23	0.19	0.22	0.13
7064	0.40	0.31	0.30	0.16
7065	0.35	0.27	0.22	0.15
7066	0.34	0.26	0.23	0.13
7067	0.33	0.24	0.20	0.14
7068	0.29	0.22	0.19	0.12
7069	0.36	0.17	0.19	0.10
7070	0.30	0.24	0.20	0.16
Mean	0.329	0.241	0.217	0.139
SD	0.046	0.040	0.031	0.019
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

0 mg/kg/day Group 1	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7011	0.12	0.08	0.13	0.03
7012	0.22	0.13	0.15	0.04
7013	0.10	0.33	0.14	0.04
7014	0.27	-0.01	0.19	0.03
7015	0.19	0.09	0.19	0.07
7016	0.20	0.13	0.10	0.19
7017	0.16	0.13	0.13	0.11
7018	0.20	0.18	0.23	0.05
7019	0.25	0.19	0.04	0.14
7020	0.22	0.24	0.19	0.09
Mean	0.193	0.148	0.149	0.080
SD	0.055	0.093	0.057	0.052
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

512 mg/kg/day Group 2	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7031	0.20	0.14	0.05	0.08
7032	0.16	0.09	0.11	0.09
7033	0.23	0.08	0.13	0.08
7034	0.18	0.12	0.07	0.08
7035	0.23	0.18	0.08	0.12
7036	0.29	0.12	0.11	0.12
7037	0.12	0.10	0.03	0.07
7038	0.21	0.12	0.10	0.12
7039	0.24	0.19	-0.01	0.14
7040	0.28	0.14	0.08	0.21
Mean	0.215	0.128	0.077	0.111
SD	0.052	0.037	0.042	0.041
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Food Efficiency

1024 mg/kg/day Group 3	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7051	0.23	0.10	0.07	0.15
7052	0.25	0.19	0.07	0.11
7053	0.21	0.15	0.13	0.13
7054	0.21	0.16	0.11	0.09
7055	0.19	0.08	0.22	0.07
7056	0.28	0.17	0.13	0.07
7057	0.16	0.15	0.14	0.13
7058	0.25	0.14	0.11	0.07
7059	0.27	0.18	0.10	0.14
7060	0.20	0.14	0.06	0.14
Mean	0.226	0.146	0.112	0.109
SD	0.037	0.033	0.049	0.033
N	10	10	10	10

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

1536 mg/kg/day Group 4	Day(s) Relative to Start Date			
	0 → 7	7 → 14	14 → 21	21 → 28
7071	0.23	0.12	0.22	0.06
7072	0.24	0.18	0.09	0.13
7073	0.23	0.18	0.09	0.15
7074	0.14	0.15	0.11	0.04
7075	0.19	0.13	0.08	0.09
7076	0.22	0.21	0.17	0.02
7077	0.23	0.19	0.14	0.09
7078	0.23	0.16	0.08	0.10
7079	0.15	0.23	0.09	0.03
7080	0.19	0.11	0.19	0.12
Mean	0.206	0.165	0.126	0.083
SD	0.038	0.040	0.052	0.044
N	10	10	10	10

APPENDIX M: INDIVIDUAL ANIMAL MEAN DAILY DIETARY INTAKE OF SOY LEGHEMOGLOBIN PREPARATION[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Dietary Intake Variable (mg/kg/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7001	0	0	0	0	0
7002	0	0	0	0	0
7003	0	0	0	0	0
7004	0	0	0	0	0
7005	0	0	0	0	0
7006	0	0	0	0	0
7007	0	0	0	0	0
7008	0	0	0	0	0
7009	0	0	0	0	0
7010	0	0	0	0	0
Mean	0.0	0.0	0.0	0.0	0.0
SD	0.0	0.0	0.0	0.0	0.0
N	10	10	10	10	10

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

512 mg/kg/day Group 2	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7021	482	544	512	492	480
7022	469	516	482	471	459
7023	468	526	476	458	456
7024	466	533	486	472	464
7025	480	551	500	511	484
7026	487	542	482	493	474
7027	474	521	493	492	468
7028	503	556	533	546	507
7029	489	519	492	468	463
7030	535	598	576	557	535
Mean	485.4	540.5	503.2	495.9	478.9
SD	20.9	24.5	30.7	33.2	24.7
N	10	10	10	10	10

Individual Animal Mean Dietary Intake.

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7041	928	1188	1129	1034	1009
7042	866	1083	1020	929	919
7043	989	1142	1089	1010	1001
7044	967	1065	993	905	925
7045	1011	1172	1012	1048	1003
7046	954	1079	921	946	919
7047	981	1079	998	948	946
7048	979	1081	992	929	937
7049	992	1032	954	975	934
7050	998	1037	965	1006	952
Mean	966.5	1095.9	1007.2	973.0	954.7
SD	42.5	53.5	61.7	49.1	36.0
N	10	10	10	10	10

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7061	1338	1587	1463	1411	1373
7062	1374	1623	1489	1424	1397
7063	1435	1745	1669	1576	1516
7064	1327	1504	1389	1303	1302
7065	1421	1569	1458	1417	1388
7066	1463	1617	1496	1450	1425
7067	1529	1631	1488	1471	1449
7068	1659	1776	1620	1603	1576
7069	1516	1625	1544	1565	1487
7070	1537	1638	1521	1518	1469
Mean	1459.8	1631.5	1513.7	1473.9	1438.2
SD	103.0	78.9	81.1	92.5	78.6
N	10	10	10	10	10

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7011	0	0	0	0	0
7012	0	0	0	0	0
7013	0	0	0	0	0
7014	0	0	0	0	0
7015	0	0	0	0	0
7016	0	0	0	0	0
7017	0	0	0	0	0
7018	0	0	0	0	0
7019	0	0	0	0	0
7020	0	0	0	0	0
Mean	0.0	0.0	0.0	0.0	0.0
SD	0.0	0.0	0.0	0.0	0.0
N	10	10	10	10	10

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day)

512 mg/kg/day Group 2	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7031	451	550	484	480	480
7032	498	622	543	523	532
7033	472	513	517	470	481
7034	510	552	557	513	521
7035	480	523	491	460	476
7036	470	513	487	451	469
7037	608	637	652	568	601
7038	474	490	495	422	458
7039	505	506	481	477	481
7040	513	513	481	458	477
Mean	498.0	541.9	518.8	482.4	497.8
SD	43.5	49.9	53.9	41.9	42.8
N	10	10	10	10	10

Individual Animal Mean Dietary Intake.

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day)

1024 mg/kg/day Group 3	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7051	1013	1082	1046	1087	1022
7052	1004	1037	980	1033	982
7053	1003	1077	1041	968	986
7054	971	1044	1012	957	963
7055	957	1102	999	910	956
7056	1035	1119	1015	948	998
7057	1004	1066	1018	1018	988
7058	960	1004	977	1003	956
7059	975	1014	979	955	948
7060	1038	1104	1083	1061	1035
Mean	995.9	1064.6	1015.1	994.0	983.4
SD	29.2	39.2	34.3	56.0	29.0
N	10	10	10	10	10

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day)

1536 mg/kg/day Group 4	Day(s) Relative to Start Date				
	0 → 7	7 → 14	14 → 21	21 → 28	0 → 28
7071	1411	1475	1479	1434	1402
7072	1431	1461	1496	1473	1418
7073	1350	1565	1455	1380	1388
7074	1405	1679	1560	1511	1489
7075	1504	1643	1597	1553	1524
7076	1610	1683	1548	1499	1534
7077	1391	1521	1456	1323	1376
7078	1584	1717	1670	1524	1573
7079	1421	1499	1421	1372	1384
7080	1703	1804	1690	1534	1618
Mean	1481.1	1604.6	1537.2	1460.2	1470.4
SD	115.0	116.7	92.3	79.0	88.2
N	10	10	10	10	10

APPENDIX N: CLINICAL PATHOLOGY

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

Submitted by:

Dupont Haskell Global Centers
for Health and Environmental Sciences
P.O. Box 30, Elkton Road
Newark, Delaware 19714

STUDY TITLE:	Clinical Pathology Results for Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats
AUTHOR:	Denise Hoban, B.A., MLT (ASCP)
CLINICAL PATHOLOGY RESULTS COMPLETED:	July 20, 2017
PERFORMING LABORATORY:	E.I. du Pont de Nemours and Company DuPont Haskell Global Centers for Health & Environmental Sciences P.O. Box 30 Newark, Delaware 19714 U.S.A.
WORK REQUEST NUMBER:	21641
SERVICE CODE NUMBER:	1611
CLIENT:	Product Safety Labs 2394 U.S. Highway 130 Dayton, New Jersey 08810 U.S.A.
CLIENT STUDY NUMBER:	43166

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The work performed at DuPont Haskell was conducted in compliance with U.S. FDA (21 CFR part 58) Good Laboratory Practice Standards, which are compatible with current OECD Good Laboratory Practices.

Client: Product Safety Labs
2394 U.S. Highway 130
Dayton, New Jersey 08810
U.S.A.

(b) (6)

Reported by: [redacted] 20 July 2017
Date

Denise Hoban, B.A., MLT (ASCP)
Senior Staff Toxicologist & Pathology Coordinator
E.I. du Pont de Nemours and Company

QUALITY ASSURANCE STATEMENT

Work Request Number: 21641
Service Code Number: 1611
PSL Study Number: 43166

Key inspections for the above referenced clinical pathology study were completed by the Quality Assurance Unit of DuPont Haskell and the findings were submitted on the following dates:

	Date Reported to:			
Audit Dates	***Principal Investigator (PI)***	***PI Management***	***Study Director (SD)***	***SD Management***
Protocol/Conduct:				
20 October 2016	21 October 2016	21 October 2016	21 October 2016	21 October 2016
Report/Records:				
29-30 November 2016	30 November 2016	30 November 2016	30 November 2016	30 November 2016
9 December 2016	9 December 2016	9 December 2016	9 December 2016	9 December 2016

(b) (6)

Reported by: [redacted] 20 - July 2017
Date

Jessica Garcia-Arbuet
Quality Assurance Auditor

CERTIFICATION

I, the undersigned, declare that these results provide accurate data obtained from this study.

(b) (6)

Issued by
Principal Investigator: [redacted] 20 July 2017

Denise Hoban, B.A., MLT (ASCP)
Senior Staff Toxicologist & Pathology Coordinator

Date

STUDY DESIGN

A 28-day dietary study in rats was conducted at Product Safety Labs (Dayton, New Jersey, U.S.A.) on behalf of Impossible Foods, Inc. (Redwood City, California, U.S.A.). Groups of 10 male and 10 female rats were fed 0, 512, 1024, 1536 mg/kg/day Soy Leghemoglobin Preparation which corresponds to 0, 250, 500 and 750 mg/kg/day of active ingredient Soy Leghemoglobin. Samples were collected for clinical pathology evaluation on test days 22 and 29/30 and were shipped to DuPont Haskell for analysis.

MATERIALS AND METHODS

Clinical pathology analyses were conducted on samples collected on test days 22 (hematology, clinical chemistry, and urinalysis) and test days 29 (males) and 30 (females) (coagulation). Hematology measurements were conducted on whole blood on the day of collection. Clinical chemistry and coagulation measurements were conducted on samples that were frozen until analysis. All blood samples were evaluated for quality by visual examination. Urinalysis measurements were conducted on the day of collection.

1. Hematology and Coagulation

Complete blood counts, including reticulocytes, were determined on an Advia 120 Hematology Analyzer. Blood smears, stained with New Methylene-Blue or Wright-Giemsa, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex CA-1500 Coagulation Analyzer.

The following parameters were determined:

red blood cell count	red cell distribution width
hemoglobin	absolute reticulocyte count
hematocrit	platelet count
mean corpuscular (cell) volume	white blood cell count
mean corpuscular (cell) hemoglobin	differential white blood cell count
mean corpuscular (cell) hemoglobin concentration	
prothrombin time	activated partial thromboplastin time

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on an Olympus AU640 Clinical Chemistry Analyzer.

The following parameters were determined:

aspartate aminotransferase	glucose
alanine aminotransferase	total protein

sorbitol dehydrogenase	albumin
alkaline phosphatase	globulin
total bilirubin	calcium
urea nitrogen	inorganic phosphorus
creatinine	sodium
cholesterol	potassium
triglycerides	chloride

3. Urinalysis

Urine volume was measured, and appearance (quality, color, and clarity) was evaluated visually. Urine protein was measured on an Olympus AU640 Clinical Chemistry Analyzer. Other urine constituents were semi-quantitatively measured on a Clinitek Atlas Automated Urine Chemistry analyzer. Sediments from urine specimens were evaluated microscopically.

The following parameters were determined:

quality	ketone
color	bilirubin
clarity	blood
volume	urobilinogen
specific gravity	protein
pH	microscopic urine sediment examination
glucose	

STATISTICAL ANALYSES

Significance was judged at $p < 0.05$. Separate analyses were performed on the data collected for each sex. Statistical analyses were performed by Provantis®.[1]

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Clinical Pathology[a]	Levene's test for homogeneity[2] and Shapiro-Wilk test[3] for normality	One-way analysis of variance[4] followed by Dunnett's test[5]	Transforms of the data to achieve normality and variance homogeneity were used. The order of transforms attempted was log, square-root, and rank-order. If the log and square-root transforms failed, the rank-order was used.

a When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.10, 0.05 was used for any calculations performed with those bilirubin data. When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.100, 1.100 was used for any calculations performed with those specific gravity data.

RECORDS AND SAMPLE STORAGE

For the work conducted at DuPont Haskell, specimens (if applicable), raw data, and the clinical pathology report will be returned to the client within 6 months after the final report issues.

REFERENCES

1. Provantis® (2012). Tables and Statistics (version 8). Instem LSS, Staffordshire, U.K.

2. Levene, H. (1960). Robust test for equality of variances. *Contributions to Probability and Statistics* (J. Olkin, ed.), pp 278-292. Stanford University Press, Palo Alto.

3. Shapiro, S.S. and Wilk, M.B. (1965). An analysis of variance test for normality (complete samples). *Biometrika* **52**, 591-611.

4. Snedecor, G.W. and Cochran, W.G. (1967). *Statistical Methods*, 6th edition, pp 246-248 and 349-352. The Iowa State University Press, Iowa.

5. Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics* **20**, 482-491.

TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

General

SD	-	standard deviation
N	-	number of values used in calculation
% Diff	-	percent difference from control
. or --	-	no data

Summary of Hematology Values

RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular (cell) volume
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
RDW	-	red cell distribution width
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell
ARET	-	absolute reticulocyte

Summary of Coagulation Values

PT	-	prothrombin time
APTT	-	activated partial thromboplastin time

Summary of Clinical Chemistry Values

AST	-	aspartate aminotransferase
ALT	-	alanine aminotransferase
SDH	-	sorbitol dehydrogenase
ALKP	-	alkaline phosphatase
BILI	-	total bilirubin
BUN	-	urea nitrogen
CREA	-	creatinine
CHOL	-	cholesterol
TRIG	-	triglycerides
GLUC	-	glucose
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
CALC	-	calcium
IPHS	-	inorganic phosphorous
NA	-	sodium
K	-	potassium
CL	-	chloride

Summary of Urinalysis Values

UVOL	-	volume
pH	-	the logarithm of the reciprocal of the hydrogen ion concentration
SG	-	specific gravity
URO	-	urobilinogen
UMTP	-	protein

TABLES

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

NOTES:

Summary of Hematology Values
Summary of Coagulation Values
Summary of Clinical Chemistry Values
Summary of Urinalysis Values

Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

The calculation for %Diff (deviation from control) is as follows:

%Diff = ((current group mean - control group mean) / control group mean) x 100

This calculation is performed upon full precision means and not the rounded values displayed within this report.

Calculation of mean, SD, and %Diff may vary from computer-generated values due to differences in rounding.

Table 1
Summary of Hematology Values for Male Rats

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
RBC (x10^6/µL)	22	Mean	7.72	7.60	7.61	7.70
		SD	0.23	0.34	0.35	0.27
		N	10	10	10	10
		%Diff		-1.6	-1.5	-0.3
HGB (g/dL)	22	Mean	15.6	15.4	15.5	15.9
		SD	0.3	0.8	0.6	0.4
		N	10	10	10	10
		%Diff		-1.5	-1.0	1.4
HCT (%)	22	Mean	45.5	45.1	45.1	45.9
		SD	0.9	1.5	1.7	0.8
		N	10	10	10	10
		%Diff		-0.9	-0.8	1.0
MCV (fL)	22	Mean	58.9	59.3	59.3	59.7
		SD	1.0	2.3	1.5	1.9
		N	10	10	10	10
		%Diff		0.7	0.7	1.3
MCH (pg)	22	Mean	20.3	20.3	20.4	20.6
		SD	0.5	0.9	0.5	0.7
		N	10	10	10	10
		%Diff		0.2	0.6	1.6
MCHC (g/dL)	22	Mean	34.4	34.2	34.4	34.5
		SD	0.4	0.4	0.3	0.5
		N	10	10	10	10
		%Diff		-0.5	-0.1	0.4
RDW (%)	22	Mean	12.1	12.5	12.5	12.3
		SD	0.3	0.5	0.3	0.5
		N	10	10	10	10
		%Diff		3.0	3.3	1.6
PLT (x10^3/µL)	22	Mean	1160	1202	1171	1227
		SD	121	89	76	185
		N	10	10	10	10
		%Diff		3.6	1.0	5.8

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Table 1
Summary of Hematology Values for Male Rats (Continued)

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
WBC (x10^3/µL)	22	Mean	13.00	14.41	11.13	13.45
		SD	1.33	2.67	1.82	4.41
		N	10	10	10	10
		%Diff		10.8	-14.4	3.4
ANEU (x10^3/µL)	22	Mean	1.91	1.99	1.75	1.57
		SD	0.67	0.43	0.43	0.62
		N	10	10	10	10
		%Diff		4.1	-8.1	-17.8
ALYM (x10^3/µL)	22	Mean	10.49	11.79	8.86	11.29
		SD	1.17	2.48	1.70	4.15
		N	10	10	10	10
		%Diff		12.4	-15.5	7.7
AMON (x10^3/µL)	22	Mean	0.31	0.34	0.28	0.30
		SD	0.10	0.11	0.05	0.10
		N	10	10	10	10
		%Diff		10.2	-9.8	-1.5
AEOS (x10^3/µL)	22	Mean	0.12	0.13	0.11	0.11
		SD	0.04	0.08	0.04	0.05
		N	10	10	10	10
		%Diff		4.4	-7.2	-7.6
ABAS (x10^3/µL)	22	Mean	0.09	0.09	0.07	0.10
		SD	0.03	0.04	0.02	0.06
		N	10	10	10	10
		%Diff		-5.0	-27.0	0.2
ALUC (x10^3/µL)	22	Mean	0.08	0.08	0.06	0.08
		SD	0.03	0.03	0.02	0.04
		N	10	10	10	10
		%Diff		-8.1	-27.0	-2.4
ARET (x10^3/µL)	22	Mean	232.6	235.8	246.3	243.8
		SD	31.2	40.7	24.1	41.1
		N	10	10	10	10
		%Diff		1.4	5.9	4.8

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

Table 2
Summary of Hematology Values for Female Rats

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
RBC (x10^6/uL)	22	Mean	7.59	8.01 *1	7.86	7.63
		SD	0.24	0.38	0.24	0.30
		N	10	10	10	10
		%Diff		5.6	3.6	0.6
HGB (g/dL)	22	Mean	15.3	16.2 *1	15.7	15.5
		SD	0.5	0.5	0.4	0.6
		N	10	10	10	10
		%Diff		5.7	2.5	0.9
HCT (%)	22	Mean	43.6	45.9 *1	44.7	44.0
		SD	1.2	1.2	1.3	1.7
		N	10	10	10	10
		%Diff		5.2	2.4	0.9
MCV (fL)	22	Mean	57.5	57.4	56.8	57.7
		SD	1.1	2.2	1.2	2.2
		N	10	10	10	10
		%Diff		-0.2	-1.1	0.4
MCH (pg)	22	Mean	20.2	20.2	20.0	20.3
		SD	0.3	0.7	0.5	0.7
		N	10	10	10	10
		%Diff		0.1	-1.0	0.3
MCHC (g/dL)	22	Mean	35.2	35.3	35.2	35.2
		SD	0.7	0.3	0.4	0.5
		N	10	10	10	10
		%Diff		0.3	0.1	0.0
RDW (%)	22	Mean	11.3	11.3	11.2	11.5
		SD	0.4	0.5	0.3	0.5
		N	10	10	10	10
		%Diff		0.1	-0.4	1.7
PLT (x10^3/uL)	22	Mean	1190	1176	1230	1229
		SD	108	127	115	114
		N	10	10	10	10
		%Diff		-1.1	3.4	3.3

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Table 2
Summary of Hematology Values for Female Rats (Continued)

Sex Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
WBC (x10^3/µL)	22	Mean	10.08	11.87	11.59	10.19
		SD	1.70	1.75	3.35	3.72
		N	10	10	10	10
		%Diff		17.7	15.0	1.1
ANEU (x10^3/µL)	22	Mean	1.48	1.56	1.68	1.54
		SD	0.30	0.58	0.85	1.10
		N	10	10	10	10
		%Diff		5.3	13.9	4.0
ALYM (x10^3/µL)	22	Mean	8.15	9.74	9.29	8.71
		SD	1.58	1.43	2.71	2.88
		N	10	10	10	10
		%Diff		19.5	14.0	0.7
AMON (x10^3/µL)	22	Mean	0.25	0.29	0.33	0.22
		SD	0.15	0.08	0.15	0.14
		N	10	10	10	10
		%Diff		16.7	32.5	-11.1
AEOS (x10^3/µL)	22	Mean	0.11	0.13	0.15	0.12
		SD	0.03	0.04	0.05	0.06
		N	10	10	10	10
		%Diff		21.4	35.8	9.0
ABAS (x10^3/µL)	22	Mean	0.04	0.07 #'	0.06	0.05
		SD	0.01	0.03	0.03	0.04
		N	10	10	10	10
		%Diff		93.2	64.1	46.7
ALUC (x10^3/µL)	22	Mean	0.05	0.07	0.07	0.05
		SD	0.02	0.02	0.03	0.04
		N	10	10	10	10
		%Diff		29.1	26.2	2.9
ARET (x10^3/µL)	22	Mean	205.8	182.4	169.1 #'	184.2
		SD	33.9	32.9	30.9	33.7
		N	10	10	10	10
		%Diff		-11.3	-17.8	-10.5

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Table 3
Summary of Coagulation Values for Male Rats

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
PT (sec)	29	Mean	10.7	10.7	10.6	10.8
		SD	0.3	0.4	0.2	0.2
		N	10	10	10	10
APTT (sec)	29	Mean	20.2	23.8	24.9 @1	23.9 @1
		SD	2.4	5.3	6.9	4.8
		N	10	10	10	10

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [@ - Test: Dunnett Non-Parametric 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Table 4
Summary of Coagulation Values for Female Rats

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
PT (sec)	30	Mean	10.0	9.8	10.0	9.8
		SD	0.2	0.2	0.3	0.2
		N	10	10	10	10
APTT (sec)	30	Mean	21.9	20.0	20.8	19.4
		SD	2.5	3.1	5.9	1.9
		N	10	10	10	10

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

Table 5
Summary of Clinical Chemistry Values for Male Rats

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
AST (U/L)	22	Mean	73	76	79	78
		SD	8	9	7	8
		N	5	9	6	8
		%Diff		4.0	7.5	6.9
ALT (U/L)	22	Mean	29	28	28	30
		SD	4	4	3	4
		N	10	10	10	10
		%Diff		-3.1	-2.4	2.4
SDH (U/L)	22	Mean	8.2	8.1	8.4	8.0
		SD	1.4	1.7	2.4	1.4
		N	5	9	6	8
		%Diff		-0.8	2.7	-1.9
ALKP (U/L)	22	Mean	183	216	216	205
		SD	24	29	44	42
		N	10	10	10	10
		%Diff		18.6	18.5	12.3
BILI (mg/dL)	22	Mean	0.17	0.17	0.18	0.18
		SD	0.02	0.02	0.02	0.02
		N	10	10	10	10
		%Diff		1.2	4.1	5.9
BUN (mg/dL)	22	Mean	10	11	10	11
		SD	1	1	1	2
		N	10	10	10	10
		%Diff		4.8	-3.8	1.0
CREA (mg/dL)	22	Mean	0.22	0.23	0.23	0.21
		SD	0.01	0.02	0.02	0.02
		N	10	10	10	10
		%Diff		3.6	4.1	-5.9
CHOL (mg/dL)	22	Mean	76	73	72	67
		SD	16	27	14	12
		N	10	10	10	10
		%Diff		-3.4	-5.4	-11.7

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

Table 5
Summary of Clinical Chemistry Values for Male Rats (Continued)

Sex Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
TRIG (mg/dL)	22	Mean	66	67	67	68
		SD	17	13	17	28
		N	10	10	10	10
		%Diff		1.6	0.9	2.4
GLUC (mg/dL)	22	Mean	95	100	102	98
		SD	12	9	13	8
		N	10	10	10	10
		%Diff		5.4	7.1	2.6
TP (g/dL)	22	Mean	6.0	6.1	6.2	6.0
		SD	0.2	0.2	0.2	0.2
		N	10	10	10	10
		%Diff		0.7	2.8	0.2
ALB (g/dL)	22	Mean	3.1	3.2	3.3 *	3.2
		SD	0.1	0.1	0.1	0.1
		N	10	10	10	10
		%Diff		2.2	4.1	1.9
GLOB (g/dL)	22	Mean	2.9	2.8	2.9	2.8
		SD	0.1	0.2	0.1	0.2
		N	10	10	10	10
		%Diff		-1.0	1.4	-1.7
CALC (mg/dL)	22	Mean	10.4	10.4	10.4	10.5
		SD	0.2	0.2	0.2	0.2
		N	10	10	10	10
		%Diff		-0.1	0.1	0.8
PHOS (mg/dL)	22	Mean	8.8	8.7	8.8	8.6
		SD	0.4	0.4	0.9	0.4
		N	5	9	8	8
		%Diff		0.6	2.1	-0.3
NA (mmol/L)	22	Mean	140.5	142.1	141.1	141.7
		SD	4.2	0.6	0.7	0.8
		N	10	10	10	10
		%Diff		1.1	0.4	0.9

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Table 5
Summary of Clinical Chemistry Values for Male Rats (Continued)

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
K (mmol/L)	22	Mean	5.03	5.19	5.55 *1	5.10
		SD	0.25	0.26	0.81	0.25
		N	10	10	10	10
		%Diff		3.1	10.4	1.4
CL (mmol/L)	22	Mean	100.8	102.0	101.6	101.7
		SD	2.4	1.0	0.9	1.2
		N	10	10	10	10
		%Diff		1.2	0.8	0.9

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [* - Test: Dunnett 2 Sided p < 0.05]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Table 6
Summary of Clinical Chemistry Values for Female Rats

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
AST (U/L)	22	Mean	69	69	64	65
		SD	6	10	8	6
		N	9	9	10	10
		%Diff		-0.3	-7.4	-6.5
ALT (U/L)	22	Mean	25	26	25	27
		SD	4	5	8	5
		N	10	10	10	10
		%Diff		2.8	-0.4	5.2
SDH (U/L)	22	Mean	8.7	8.1	8.0	9.9
		SD	2.2	1.2	0.9	2.5
		N	9	9	10	10
		%Diff		-7.4	-9.0	12.9
ALKP (U/L)	22	Mean	137	107 #1	121	108 #1
		SD	16	19	29	25
		N	10	10	10	10
		%Diff		-22.4	-12.1	-21.3
BILI (mg/dL)	22	Mean	0.18	0.19	0.20	0.19
		SD	0.02	0.02	0.02	0.03
		N	10	10	10	10
		%Diff		8.4	10.6	7.8
BUN (mg/dL)	22	Mean	12	11	12	12
		SD	2	1	2	1
		N	10	10	10	10
		%Diff		-11.5	-0.8	0.0
CREA (mg/dL)	22	Mean	0.28	0.26	0.27	0.28
		SD	0.02	0.02	0.03	0.03
		N	10	10	10	10
		%Diff		-6.9	-2.9	1.1
CHOL (mg/dL)	22	Mean	85	95	98	94
		SD	11	18	19	22
		N	10	10	10	10
		%Diff		12.2	15.6	11.7

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Table 6
Summary of Clinical Chemistry Values for Female Rats (Continued)

Sex Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
TRIG (mg/dL)	22	Mean	37	38	48	35
		SD	6	9	15	8
		N	10	10	10	10
		%Diff		3.5	24.9	-4.3
GLUC (mg/dL)	22	Mean	118	103 #1	104 #1	110
		SD	15	10	10	14
		N	10	10	10	10
		%Diff		-13.3	-12.0	-6.7
TP (g/dL)	22	Mean	6.4	6.7	6.8	6.7
		SD	0.3	0.4	0.3	0.4
		N	10	10	10	10
		%Diff		5.1	5.6	3.7
ALB (g/dL)	22	Mean	3.5	3.7	3.7	3.6
		SD	0.2	0.2	0.2	0.3
		N	10	10	10	10
		%Diff		4.0	4.6	3.4
GLOB (g/dL)	22	Mean	2.9	3.1	3.1 #1	3.0
		SD	0.1	0.2	0.2	0.1
		N	10	10	10	10
		%Diff		6.6	6.9	4.1
CALC (mg/dL)	22	Mean	10.5	10.9 #1	11.0 #1	10.7
		SD	0.3	0.3	0.3	0.4
		N	10	10	10	10
		%Diff		3.8	5.1	1.8
IPHS (mg/dL)	22	Mean	7.1	7.8	7.6	7.1
		SD	0.5	0.6	0.4	0.8
		N	9	9	10	10
		%Diff		9.7	6.5	-0.6
NA (mmol/L)	22	Mean	140.3	140.6	140.3	140.2
		SD	1.1	0.6	0.7	1.1
		N	10	10	10	10
		%Diff		0.2	0.0	0.0

General Footnote [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test Dunnett 2 Sided p < 0.05]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Table 6
Summary of Clinical Chemistry Values for Female Rats (Continued)

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
K (mmol/L)	22	Mean	4.56	4.63	4.72	4.74
		SD	0.33	0.38	0.21	0.38
		N	10	10	10	10
		%Diff		1.5	3.5	4.0
CL (mmol/L)	22	Mean	102.6	101.3 #*	101.1 #*	102.1
		SD	1.2	1.4	1.0	1.1
		N	10	10	10	10
		%Diff		-1.3	-1.5	-0.5

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Table 7
Summary of Urinalysis Values for Male Rats

Sex: Male	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
UVOL (mL)	22	Mean	11.7	11.5	12.3	14.3
		SD	8.2	9.8	7.3	7.7
		N	10	10	10	10
		%Diff		-1.8	4.8	22.0
pH	22	Mean	6.5	6.5	6.6	6.6
		SD	0.3	0.4	0.4	0.4
		N	10	9	10	10
		%Diff		0.0	0.8	1.5
SG	22	Mean	1.027	1.027	1.026	1.024
		SD	0.019	0.015	0.015	0.019
		N	10	9	10	10
		%Diff		0.0	-0.1	-0.3
URO (EU/dL)	22	Mean	0.3	0.2	0.3	0.2
		SD	0.3	0.0	0.3	0.0
		N	10	9	10	10
		%Diff		-28.6	0.0	-28.6
UMTP (mg/dL)	22	Mean	104	241	124	111
		SD	49	365	80	97
		N	10	10	10	10
		%Diff		132.5	19.5	7.4

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Table 8
Summary of Urinalysis Values for Female Rats

Sex: Female	Day(s) Relative to Start Date		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
UVOL (mL)	22	Mean	7.9	6.8	6.5	6.8
		SD	6.4	5.1	3.0	4.1
		N	10	10	10	10
		%Diff		-12.3	-15.9	-14.9
pH	22	Mean	6.4	6.2	6.6	6.5
		SD	0.4	0.4	0.6	0.6
		N	10	10	10	10
		%Diff		-3.9	3.1	0.8
SG	22	Mean	1.037	1.035	1.028	1.030
		SD	0.027	0.023	0.011	0.013
		N	10	10	10	10
		%Diff		-0.2	-0.8	-0.6
URO (EU/dL)	22	Mean	0.2	0.2	0.2	0.3
		SD	0.0	0.0	0.0	0.3
		N	10	10	10	10
		%Diff		0.0	0.0	40.0
UMTP (mg/dL)	22	Mean	43	41	34	44
		SD	34	25	12	30
		N	10	10	10	10
		%Diff		-3.7	-20.0	3.5

General Footnote [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Appendix A
Individual Animal Clinical Pathology Data

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

General:

-	-	not observed
.	-	not taken, not performed, not observed, or results not valid
Man	-	many
Mod	-	moderate
NPH	-	not performed due to hemolysis
OK	-	sample condition OK for testing
ppm	-	parts per million
QNS	-	sample quantity not sufficient for testing

Individual Hematology Values:

WB	-	whole blood condition
RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular (cell) volume
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
RDW	-	red cell distribution width
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell
ARET	-	absolute reticulocyte

Individual Coagulation Values:

PHEM	-	plasma hemolysis
PLIP	-	plasma lipemia
PICT	-	plasma icterus
PT	-	prothrombin time
APTT	-	activated partial thromboplastin time

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Individual Clinical Chemistry Values:
- HEM - hemolysis
- LIP - lipemia
- ICT - icterus
- AST - aspartate aminotransferase
- ALT - alanine aminotransferase
- SDH - sorbitol dehydrogenase
- ALKP - alkaline phospharase
- BILI - total bilirubin
- BUN - urea nitrogen
- CREA - creatinine
- CHOL - cholesterol
- TRIG - triglycerides
- GLUC - glucose
- TP - total protein
- ALB - albumin
- GLOB - globulin
- CALC - calcium
- IPHS - inorganic phosphorous
- NA - sodium
- K - potassium
- CL - chloride

Individual Urinalysis Values:
- QUAL - quality (modifies color)
- COL - color
- CLAR - clarity
- UVOL - volume
- pH - the logarithm of the reciprocal of the hydrogen ion concentration
- SG - specific gravity
- UGLC - Glucose
- KET - ketone
- UBIL - bilirubin
- BLD - blood
- URO - urobilinogen
- UMTP - protein

Individual Urine Microscopic Examination Values:
- EPIT - epithelial cells
- UWBC - urine white blood cells
- URBC - urine red blood cells
- NCRY - normal crystals
- MICR - microorganisms
- SPER - sperm
- REPI - renal epithelial cell
- MUC - mucus strand

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons:
the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

Only positive findings were recorded for special observations (e.g., additional cell types) or observations marked other.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	CBC/DIFF/RETIC Cont. WB	RBC (x10^6/µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
	22	22	22	22	22	22	22
7001	OK	7.48	15.5	44.6	59.6	20.8	34.9
7002	OK	7.69	15.2	44.5	57.9	19.8	34.2
7003	OK	7.65	15.5	45.1	58.9	20.3	34.5
7004	OK	8.10	16.1	47.5	58.7	19.9	33.9
7005	OK	7.69	15.5	45.0	58.6	20.1	34.3
7006	OK	7.37	15.4	45.0	61.0	20.9	34.3
7007	OK	7.55	15.4	45.1	59.7	20.5	34.2
7008	OK	7.95	15.6	45.6	57.4	19.6	34.1
7009	OK	7.79	16.2	45.8	58.8	20.8	35.3
7010	OK	7.96	16.0	46.5	58.4	20.6	34.3

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	CBC/DIFF/RETIC Cont. RDW (%)	PLT (x10^3/µL)	WBC (x10^3/µL)	ANEU (x10^3/µL)	ALYM (x10^3/µL)	AMON (x10^3/µL)	ABAS (x10^3/µL)
	22	22	22	22	22	22	22
7001	12.0	1128	15.34	2.24	12.17	0.31	0.11
7002	11.7	1118	11.88	1.52	9.71	0.31	0.22
7003	11.9	1217	10.89	1.20	9.30	0.16	0.08
7004	12.2	1078	13.86	3.17	10.19	0.29	0.13
7005	12.8	1229	14.23	1.34	12.39	0.18	0.07
7006	12.1	992	13.27	1.69	10.75	0.50	0.15
7007	12.0	1076	12.24	1.35	10.01	0.35	0.13
7008	12.2	1142	13.54	1.95	11.08	0.22	0.09
7009	12.0	1240	11.73	1.51	9.48	0.30	0.14
7010	12.3	1406	13.02	2.92	9.08	0.36	0.13

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
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Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	ABAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7001	0.11	0.11	241.2
7002	0.06	0.06	225.6
7003	0.07	0.08	213.2
7004	0.06	0.06	233.5
7005	0.13	0.13	295.6
7006	0.04	0.13	263.3
7007	0.10	0.07	233.9
7008	0.14	0.07	197.9
7009	0.12	0.08	190.8
7010	0.10	0.04	226.2

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	CBC/DIFF/RETIC (Contd.)						
	WB	RBC (x10^6/µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
	22	22	22	22	22	22	22
7021	OK	7.66	16.6	47.6	62.0	21.6	34.8
7022	OK	8.15	15.1	45.1	55.3	18.6	33.6
7023	OK	7.74	15.3	45.3	58.5	19.8	33.9
7024	OK	7.28	14.7	42.8	58.8	20.2	34.4
7025	OK	7.10	13.9	41.7	59.0	20.1	34.0
7026	OK	7.09	14.9	43.3	61.1	21.0	34.4
7027	OK	8.06	15.7	46.2	57.3	19.5	33.9
7028	OK	7.74	15.5	44.7	57.7	20.0	34.7
7029	OK	7.52	15.7	45.9	61.0	20.9	34.3
7030	OK	7.34	15.7	46.0	62.6	21.4	34.2

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	CBC/DIFF/RETIC (Contd.)						
	RDW (%)	PLT (x10^3/µL)	WBC (x10^3/µL)	ANEU (x10^3/µL)	ALYM (x10^3/µL)	AMON (x10^3/µL)	AEOS (x10^3/µL)
	22	22	22	22	22	22	22
7021	12.7	1335	14.10	1.55	11.99	0.28	0.10
7022	12.9	1136	16.79	2.38	13.37	0.44	0.35
7023	13.0	1247	11.65	1.13	10.08	0.27	0.07
7024	12.1	1265	13.53	1.76	11.28	0.26	0.11
7025	13.2	1195	12.75	2.50	9.74	0.28	0.08
7026	12.5	1172	13.87	1.79	11.60	0.24	0.10
7027	11.7	1158	11.49	2.00	8.76	0.54	0.10
7028	12.5	1104	20.57	2.16	17.81	0.25	0.12
7029	12.1	1229	14.96	2.26	11.96	0.45	0.13
7030	12.1	1185	14.36	2.34	11.34	0.40	0.11

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
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Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	ABAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7021	0.13	0.06	252.3
7022	0.13	0.13	224.6
7023	0.07	0.05	197.6
7024	0.07	0.05	225.0
7025	0.08	0.06	265.7
7026	0.08	0.07	220.8
7027	0.05	0.06	230.8
7028	0.14	0.08	167.9
7029	0.04	0.10	234.0
7030	0.07	0.09	308.3

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day (Group 3)	CBC/DIFF/RETIC (Contd.)						
	WB	RBC (x10^6/µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
	22	22	22	22	22	22	22
7041	OK	7.74	15.2	44.6	57.6	19.6	34.1
7042	OK	[illegible]	16.1	46.7	60.2	20.8	34.5
7043	OK	7.76	15.4	45.3	58.4	19.9	34.1
7044	OK	7.72	15.9	46.7	60.5	20.6	34.1
7045	OK	7.87	16.1	46.2	58.7	20.4	34.8
7046	OK	6.75	14.1	40.7	59.9	20.8	34.8
7047	OK	7.45	15.5	45.5	61.1	20.8	34.1
7048	OK	7.25	15.2	44.4	61.2	21.0	34.3
7049	OK	7.91	15.7	45.0	56.9	19.8	34.8
7050	OK	7.81	15.7	46.0	58.9	20.2	34.2

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day (Group 3)	CBC/DIFF/RETIC (Contd.)						
	RDW (%)	PLT (x10^3/µL)	WBC (x10^3/µL)	ANEU (x10^3/µL)	ALYM (x10^3/µL)	AMON (x10^3/µL)	AEOS (x10^3/µL)
	22	22	22	22	22	22	22
7041	12.1	1206	11.55	1.64	9.45	0.25	0.08
7042	12.5	1167	14.92	2.07	12.20	0.28	0.16
7043	12.3	1228	12.44	2.31	9.52	0.37	0.11
7044	13.0	1333	10.33	1.87	7.96	0.26	0.12
7045	12.1	1007	9.46	1.94	7.03	0.29	0.11
7046	12.5	1209	11.47	1.89	8.91	0.32	0.19
7047	12.6	1159	10.04	1.58	7.95	0.31	0.10
7048	12.6	1232	12.44	1.08	10.95	0.25	0.05
7049	12.9	1123	8.79	1.03	7.34	0.22	0.07
7050	12.6	1160	9.86	2.12	7.29	0.25	0.13

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	ABAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7041	0.05	0.08	270.7
7042	0.09	0.10	228.3
7043	0.06	0.06	293.3
7044	0.06	0.04	235.3
7045	0.08	0.05	222.1
7046	0.07	0.08	265.6
7047	0.07	0.05	243.9
7048	0.06	0.05	245.0
7049	0.09	0.04	211.8
7050	0.04	0.04	241.2

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	CBC/DIFF/RETIC Cont.						
	WB	RBC	HGB	HCT	MCV	MCH	MCHC
		(x10^6/µL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)
	22	22	22	22	22	22	22
7061	OK	8.23	15.9	46.6	56.6	19.3	34.1
7062	OK	7.77	15.8	45.4	58.5	20.4	34.9
7063	OK	7.59	15.9	45.5	59.9	21.0	35.0
7064	OK	7.36	16.1	47.1	63.9	21.8	34.2
7065	OK	7.84	16.2	46.4	59.2	20.6	34.8
7066	OK	7.40	14.9	44.8	60.5	20.2	33.3
7067	OK	7.64	15.9	45.5	59.6	20.8	34.9
7068	OK	7.62	15.7	45.1	59.2	20.5	34.7
7069	OK	8.06	16.1	46.9	58.6	20.1	34.4
7070	OK	7.58	16.1	45.9	60.5	21.2	35.0

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	CBC/DIFF/RETIC Cont.						
	WB	RBC	HGB	HCT	MCV	MCH	MCHC
		(x10^6/µL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)
	22	22	22	22	22	22	22
7061	OK	8.23	15.9	46.6	56.6	19.3	34.1
7062	OK	7.77	15.8	45.4	58.5	20.4	34.9
7063	OK	7.59	15.9	45.5	59.9	21.0	35.0
7064	OK	7.36	16.1	47.1	63.9	21.8	34.2
7065	OK	7.84	16.2	46.4	59.2	20.6	34.8
7066	OK	7.40	14.9	44.8	60.5	20.2	33.3
7067	OK	7.64	15.9	45.5	59.6	20.8	34.9
7068	OK	7.62	15.7	45.1	59.2	20.5	34.7
7069	OK	8.06	16.1	46.9	58.6	20.1	34.4
7070	OK	7.58	16.1	45.9	60.5	21.2	35.0

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
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Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	ABAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7061	0.06	0.06	268.5
7062	0.09	0.04	238.4
7063	0.21	0.09	310.6
7064	0.10	0.10	319.9
7065	0.12	0.06	232.2
7066	0.05	0.07	224.8
7067	0.06	0.14	249.9
7068	0.17	0.15	194.5
7069	0.05	0.04	235.2
7070	0.05	0.06	214.2

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	CBC/DIFF RETIC Comp						
	WB	RBC (x10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
	22	22	22	22	22	22	22
7011	OK	7.71	15.7	43.5	56.4	20.4	36.3
7012	OK	7.82	15.7	44.8	57.2	20.1	35.2
7013	OK	7.22	14.8	42.4	58.8	20.5	34.9
7014	OK	7.72	15.6	44.4	57.5	20.2	35.1
7015	OK	7.33	15.0	43.3	59.2	20.5	34.7
7016	OK	7.41	14.6	42.4	57.3	19.7	34.4
7017	OK	7.93	16.1	44.5	56.1	20.4	36.3
7018	OK	7.76	15.6	45.5	58.6	20.1	34.3
7019	OK	7.67	15.4	43.5	56.7	20.1	35.5
7020	OK	7.33	14.7	41.6	56.7	20.0	35.3

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	CBC/DIFF RETIC Comp						
	RDW (%)	PLT (x10^3/uL)	WBC (x10^3/uL)	ANEU (x10^3/uL)	ALYM (x10^3/uL)	AMON (x10^3/uL)	ABOS (x10^3/uL)
	22	22	22	22	22	22	22
7011	11.2	1258	9.60	1.42	7.95	0.16	0.08
7012	10.8	1173	8.81	1.49	6.96	0.21	0.10
7013	11.1	1262	9.63	1.65	7.43	0.36	0.11
7014	11.2	1064	10.65	1.35	8.92	0.14	0.10
7015	11.2	1217	8.53	2.00	6.24	0.13	0.09
7016	11.6	1126	11.48	1.80	9.12	0.40	0.17
7017	10.8	1123	8.94	0.83	7.73	0.13	0.13
7018	12.3	1404	11.97	1.38	10.14	0.19	0.15
7019	11.1	1373	13.21	1.48	10.90	0.58	0.09
7020	11.5	1269	7.89	1.33	6.20	0.21	0.10

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1025 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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Individual Animal Clinical Pathology Data

Sex: Female   Day(s) Relative to Start Date

0 mg/kg/day Group 1	ADAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7011	0.05	0.03	151.8
7012	0.02	0.04	192.8
7013	0.02	0.06	205.3
7014	0.04	0.09	215.0
7015	0.01	0.03	243.8
7016	0.03	0.05	153.5
7017	0.03	0.04	226.8
7018	0.09	0.07	252.5
7019	0.07	0.09	194.2
7020	0.02	0.04	222.0

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
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Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	CBC/DIFF/RETIC Compl WBC	RBC (x10^6/µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
	22	22	22	22	22	22	22
2031	OK	8.35	16.2	45.4	54.4	19.4	35.6
2032	OK	8.12	16.9	47.4	56.3	20.6	35.6
2033	OK	8.13	15.5	44.5	54.8	19.1	34.8
2034	OK	7.89	16.3	46.0	58.3	20.4	34.9
2035	OK	7.09	15.7	44.5	61.0	21.5	35.3
2036	OK	7.93	16.5	46.3	58.4	20.8	35.5
2037	OK	8.48	16.5	46.4	54.8	19.5	35.6
2038	OK	7.80	16.2	46.1	59.2	20.7	35.2
2039	OK	8.21	16.7	47.7	58.1	20.4	35.1
2040	OK	7.63	15.7	44.4	58.2	20.5	35.3

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	CBC/DIFF/RETIC Compl RDW (%)	PLT (x10^3/µL)	WBC (x10^3/µL)	ANEU (x10^3/µL)	ALYM (x10^3/µL)	AMON (x10^3/µL)	ABAS (x10^3/µL)
	22	22	22	22	22	22	22
2031	11.3	1067	11.91	0.92	10.44	0.32	0.13
2032	11.8	1387	10.43	0.99	9.05	0.19	0.08
2033	11.1	1159	16.00	2.26	13.15	0.32	0.10
2034	10.5	1172	9.70	1.45	7.97	0.21	0.09
2035	11.3	1368	12.45	2.38	9.45	0.37	0.09
2036	11.4	1270	11.46	1.99	8.90	0.36	0.19
2037	10.8	1167	12.95	1.79	10.55	0.26	0.17
2038	11.9	1075	10.91	0.74	9.50	0.32	0.16
2039	11.2	1048	10.62	1.20	8.78	0.34	0.17
2040	11.8	1076	12.10	1.84	9.70	0.24	0.17

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	ABAS ($x10^3/\mu L$)	ALUC ($x10^3/\mu L$)	ARET ($x10^3/\mu L$)
	22	22	22
7031	0.07	0.06	155.8
7032	0.04	0.06	199.4
7033	0.10	0.10	205.1
7034	0.03	0.05	163.2
7035	0.06	0.06	214.8
7036	0.06	0.07	222.0
7037	0.09	0.09	133.1
7038	0.12	0.07	137.0
7039	0.07	0.05	184.7
7040	0.07	0.07	206.3

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
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Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day (Group 3)	CBC/DIFF/RETIC (Contd.) WB	RBC (x10^6/µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
	22	22	22	22	22	22	22
7051	OK	7.50	15.3	42.6	56.8	20.5	36.0
7052	OK	7.61	15.7	44.1	58.0	20.6	35.5
7053	OK	7.91	15.6	44.7	56.5	19.8	35.0
7054	OK	8.16	15.9	46.3	56.8	19.5	34.4
7055	OK	7.87	15.2	43.2	55.0	19.4	35.3
7056	OK	7.91	15.7	45.0	56.9	19.8	34.8
7057	OK	7.64	15.4	43.6	57.0	20.2	35.4
7058	OK	8.02	15.7	44.5	55.4	19.5	35.3
7059	OK	7.73	16.1	45.9	59.3	20.8	35.1
7060	OK	8.26	16.3	46.6	56.4	19.9	35.3

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day (Group 3)	CBC/DIFF/RETIC (Contd.) RDW (%)	PLT (x10^3/µL)	WBC (x10^3/µL)	ANEU (x10^3/µL)	ALYM (x10^3/µL)	AMON (x10^3/µL)	AEOS (x10^3/µL)
	22	22	22	22	22	22	22
7051	11.2	1288	7.91	1.06	6.40	0.27	0.13
7052	11.2	1253	8.44	1.37	6.68	0.20	0.15
7053	11.9	1220	12.97	2.97	9.03	0.66	0.19
7054	11.3	1063	11.78	2.33	8.91	0.32	0.06
7055	11.1	1334	8.29	1.24	6.65	0.25	0.08
7056	11.5	1162	15.10	2.02	12.16	0.50	0.23
7057	11.2	1178	12.42	0.88	11.03	0.21	0.15
7058	11.0	1305	17.73	3.07	13.88	0.37	0.18
7059	11.0	1040	13.10	0.88	11.48	0.38	0.20
7060	10.9	1303	8.10	1.07	6.55	0.15	0.15

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	ABAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7051	0.03	0.03	98.9
7052	0.03	0.03	187.5
7053	0.06	0.05	170.5
7054	0.05	0.08	160.2
7055	0.05	0.03	169.8
7056	0.11	0.11	178.7
7057	0.07	0.07	203.0
7058	0.12	0.11	164.4
7059	0.05	0.10	173.4
7060	0.03	0.04	174.5

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	CBC/DIFF/RETIC Cont.d						
	WB	RBC	HGB	HCT	MCV	MCH	MCHC
		(x10^6/µL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)
	22	22	22	22	22	22	22
7071	OK	7.57	14.7	42.2	55.7	19.4	34.9
7072	OK	7.84	15.4	44.3	56.4	19.7	34.8
7073	OK	7.32	15.4	44.8	61.2	21.0	34.4
7074	OK	7.45	15.0	42.3	56.8	20.2	35.6
7075	OK	7.95	15.6	44.0	55.4	19.7	35.5
7076	OK	7.27	15.7	43.9	60.4	21.6	35.8
7077	OK	8.12	16.7	47.1	58.0	20.6	35.5
7078	OK	7.67	16.0	46.2	60.2	20.8	34.6
7079	OK	7.82	15.2	43.1	55.1	19.4	35.3
7080	OK	7.31	14.9	42.0	57.5	20.3	35.4

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	CBC/DIFF/RETIC Cont.d						
	RDW	PLT	WBC	ANEU	ALYM	AMON	AEOS
	(%)	(x10^3/µL)	(x10^3/µL)	(x10^3/µL)	(x10^3/µL)	(x10^3/µL)	(x10^3/µL)
	22	22	22	22	22	22	22
7071	12.4	1062	12.22	3.01	8.75	0.28	0.13
7072	11.0	1262	7.01	0.79	5.93	0.13	0.12
7073	11.3	1341	17.13	4.48	12.09	0.55	0.15
7074	11.6	1235	5.39	1.19	4.01	0.09	0.03
7075	11.6	1366	10.77	1.08	9.28	0.19	0.09
7076	10.9	1360	10.86	1.12	9.35	0.20	0.10
7077	11.7	1195	10.58	1.21	8.64	0.53	0.26
7078	10.9	1258	14.13	0.92	12.69	0.21	0.17
7079	11.9	1153	7.79	0.79	6.73	0.15	0.06
7080	12.0	1052	6.06	1.20	4.65	0.07	0.10

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female   Day(s) Relative to Start Date

1536 mg/kg/day Group 4	ADAS (x10^3/µL)	ALUC (x10^3/µL)	ARET (x10^3/µL)
	22	22	22
7071	0.05	0.04	230.7
7072	0.02	0.01	179.2
7073	0.14	0.14	214.5
7074	0.01	0.03	164.1
7075	0.05	0.06	152.9
7076	0.05	0.04	176.2
7077	0.06	0.06	169.7
7078	0.10	0.10	155.2
7079	0.03	0.04	180.5
7080	0.02	0.02	238.7

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	29	29	29	29	29
7001	None	None	None	11.1	20.5
7002	None	None	None	10.6	18.6
7003	None	None	None	10.3	20.5
7004	None	None	None	10.6	25.4
7005	None	None	None	10.5	[illegible]
7006	None	None	None	10.1	22.5
7007	None	None	None	11.1	17.5
7008	None	None	None	10.9	20.2
7009	None	None	None	10.8	19.5
7010	None	None	None	10.6	19.4

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	29	29	29	29	29
7021	None	None	None	11.1	21.7
7022	None	None	None	10.6	34.6
7023	None	None	None	10.7	26.0
7024	None	None	None	10.4	19.7
7025	None	None	None	10.8	31.0
7026	None	None	None	10.7	21.5
7027	None	None	None	10.5	21.2
7028	None	None	None	11.3	22.6
7029	None	None	None	10.7	22.4
7030	None	None	None	10.0	17.5

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	29	29	29	29	29
7041	None	None	None	10.5	41.9
7042	None	None	None	10.9	27.8
7043	None	None	None	10.5	21.9
7044	None	None	None	10.7	23.9
7045	None	None	None	10.9	27.1
7046	None	None	None	10.4	22.4
7047	None	None	None	10.3	17.0
7048	None	None	None	10.7	19.9
7049	None	None	None	10.6	24.8
7050	None	None	None	10.9	26.0

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	29	29	29	29	29
7061	None	None	None	10.7	35.2
7062	None	None	None	10.7	20.0
7063	None	None	None	10.5	25.2
7064	None	None	None	10.1	23.0
7065	None	None	None	10.6	20.8
7066	None	None	None	10.2	21.8
7067	None	None	None	10.3	17.8
7068	None	None	None	10.7	21.9
7069	None	None	None	10.9	22.6
7070	None	None	None	10.7	23.3

Group 2: 512 mg/kg/day of test substance corresponds to 290 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to [illegible] mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to [illegible] mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female   Day(s) Relative to Start Date

0 mg/kg/day Group 1	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	30	30	30	30	30
7011	None	None	None	9.8	22.6
7012	None	None	None	10.4	23.4
7013	None	None	None	10.0	18.6
7014	None	None	None	10.1	21.2
7015	None	None	None	10.0	23.8
7016	None	None	None	10.1	26.8
7017	None	None	None	9.9	19.6
7018	None	None	None	10.3	22.6
7019	None	None	None	9.8	19.2
7020	None	None	None	10.2	21.3

Sex: Female   Day(s) Relative to Start Date

512 mg/kg/day Group 2	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	30	30	30	30	30
7031	None	None	None	10.0	17.3
7032	None	None	None	9.7	27.4
7033	None	None	None	9.9	16.3
7034	None	None	None	9.9	20.0
7035	None	None	None	9.5	18.1
7036	None	None	None	10.0	21.4
7037	None	None	None	9.6	19.4
7038	None	None	None	10.1	18.0
7039	None	None	None	9.6	19.0
7040	None	None	None	10.1	22.1

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	30	30	30	30	30
7061	None	None	None	10.6	[illegible]
7062	None	None	None	10.1	27.3
7063	None	None	None	9.8	14.9
7064	None	None	None	9.4	17.1
7065	None	None	None	10.0	21.3
7066	None	None	None	10.1	21.0
7067	None	None	None	9.2	23.8
7068	None	None	None	9.7	15.4
7069	None	None	None	10.2	18.3
7070	None	None	None	10.0	17.2

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	PHEM	PLIP	PICT	PT (sec)	APTT (sec)
	30	30	30	30	30
7071	None	None	None	9.7	18.2
7072	None	None	None	9.9	20.3
7073	None	None	None	9.4	17.6
7074	None	None	None	10.0	16.9
7075	None	None	None	9.7	18.3
7076	None	None	None	10.1	23.6
7077	None	None	None	9.7	20.1
7078	None	None	None	10.0	20.3
7079	None	None	None	9.9	18.8
7080	None	None	None	9.9	19.8

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Chemistry Data

Sex: Male Day(s) Relative to Start Date

(mg/kg/day) Group [illegible]	HEM	LIP	ICT	AST (U/L)	ALT (U/L)	SDH (U/L)	ALKP (U/L)
	22	22	22	22	22	22	22
7001	Trace	None	None	NPH	25	NPH	184
7002	Trace	None	None	NPH	33	NPH	162
7003	Trace	None	None	NPH	28	NPH	166
7004	None	None	None	72	26	10.3	241
7005	None	None	None	87	30	7.7	202
7006	Trace	None	None	NPH	29	NPH	181
7007	None	None	None	72	30	7.9	173
7008	Trace	None	None	NPH	28	NPH	186
7009	None	None	None	70	25	8.4	158
7010	None	None	None	65	26	6.6	172

Sex: Male Day(s) Relative to Start Date

(mg/kg/day) Group [illegible]	BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7001	0.19	12	0.23	78	53	113	6.1
7002	0.18	11	0.23	106	82	82	6.6
7003	0.19	9	0.20	84	67	88	5.9
7004	0.16	12	0.24	73	30	87	6.2
7005	0.17	11	0.23	71	50	95	6.0
7006	0.20	10	0.23	89	90	120	6.0
7007	0.14	9	0.20	85	55	92	5.6
7008	0.17	8	0.22	68	72	84	6.0
7009	0.15	11	0.20	74	40	96	6.4
7010	0.14	11	0.22	69	62	93	5.9

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	Olympus Chem Plus						
	ALB	GLOB	CALC	PHOS	NA	K	CL
	(g/dL)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)	(mmol/L)
	22	22	22	22	22	22	22
7001	3.2	2.9	10.7	NFH	143.7	4.91	102.5
7002	3.1	2.9	10.4	NFH	141.6	5.47	101.5
7003	3.1	2.8	10.5	NFH	140.9	5.02	100.8
7004	3.1	3.1	10.4	8.6	142.0	4.96	101.5
7005	3.2	2.8	10.2	9.6	142.5	4.95	101.1
7006	3.1	2.9	10.5	NFH	140.8	5.32	101.8
7007	3.0	2.6	10.0	8.1	128.9	4.91	94.0
7008	3.2	2.8	10.4	NFH	141.9	4.65	102.2
7009	3.3	3.1	10.8	8.4	141.4	5.29	101.1
7010	3.1	2.8	10.4	8.9	141.5	4.82	101.4

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

512 (mg/kg/day) Group 2	Olympus Chem Plus						
	HEM	LIP	ICT	AST (IU/L)	ALT (IU/L)	SDH (IU/L)	ALKP (IU/L)
	22	22	22	22	22	22	22
7021	None	None	None	70	30	8.0	192
7022	None	None	None	85	25	4.9	243
7023	Trace	None	None	NFH	26	NFH	218
7024	None	None	None	76	24	7.6	194
7025	None	None	None	82	29	11.6	182
7026	None	None	None	74	27	7.4	204
7027	None	None	None	81	35	8.4	264
7028	None	None	None	68	24	7.8	218
7029	None	None	None	63	27	9.1	190
7030	None	None	None	92	33	8.2	237

Sex: Male Day(s) Relative to Start Date

512 (mg/kg/day) Group 2	Olympus Chem Plus						
	BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7021	0.17	11	0.24	86	73	105	5.2
7022	0.20	11	0.26	72	77	92	5.7
7023	0.17	9	0.25	97	65	114	5.4
7024	0.18	13	0.24	51	39	100	6.1
7025	0.18	11	0.24	53	65	96	6.0
7026	0.15	12	0.20	138	69	90	5.9
7027	0.15	12	0.23	55	61	108	6.0
7028	0.15	9	0.23	29	92	91	5.3
7029	0.19	9	0.24	95	65	94	6.2
7030	0.17	12	0.23	78	66	111	5.7

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Olympus Chem Plus						
	ALB (g/dL)	GLOB (g/dL)	CALC (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
	22	22	22	22	22	22	22
7021	3.4	2.8	11.0	9.3	142.5	4.90	100.8
7022	3.1	2.6	10.5	8.3	140.6	5.05	101.2
7023	3.3	3.1	10.5	NFH	140.7	5.27	101.5
7024	3.2	2.9	10.3	8.1	140.3	5.33	103.8
7025	3.1	2.9	10.3	9.6	140.9	5.35	102.6
7026	3.1	2.8	10.4	8.6	142.0	5.34	102.6
7027	3.6	3.0	10.1	8.8	142.4	5.25	102.8
7028	3.4	2.9	10.3	8.5	143.2	5.66	102.2
7029	3.3	2.9	10.5	8.9	141.5	4.73	100.7
7030	3.2	2.5	10.3	8.4	143.0	5.18	103.9

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Olympus Chem Plus HEM	LIP	ICT	AST (U/L)	ALT (U/L)	SDH (U/L)	ALKP (U/L)
	22	22	22	22	22	22	22
7041	None	None	None	81	24	[illegible]	181
7042	None	None	None	76	28	[illegible]	206
7043	Trace	None	None	NPH	24	NPH	193
7044	None	None	None	86	28	13.0	227
7045	Trace	None	None	NPH	30	NPH	295
7046	None	None	None	69	32	8.8	236
7047	Trace	None	None	NPH	29	NPH	157
7048	None	None	None	87	25	6.9	207
7049	Trace	None	None	NPH	31	NPH	244
7050	None	None	None	73	31	[illegible]	164

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Olympus Chem Plus BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7041	0.18	10	0.22	[illegible]	72	90	5.2
7042	0.17	9	0.22	85	90	107	6.3
7043	0.17	9	0.25	70	62	101	6.5
7044	0.18	10	0.23	73	96	86	6.2
7045	0.15	11	0.26	61	65	109	6.0
7046	0.20	12	0.25	94	74	124	6.6
7047	0.17	9	0.23	[illegible]	58	102	6.1
7048	0.15	12	0.23	76	63	83	6.0
7049	0.19	8	0.20	46	41	99	6.3
7050	0.20	10	0.20	75	47	136	6.3

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Olympus Chem Pla						
	ALB (g/dL)	GLOB (g/dL)	CALC (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
	22	22	22	22	22	22	22
7041	3.3	2.9	10.5	7.5	141.6	5.30	101.2
7042	3.3	3.0	10.9	8.8	140.7	4.79	100.4
7043	3.4	3.1	10.4	NPH	142.1	4.96	101.3
7044	3.3	2.9	10.5	8.4	140.3	6.83	101.9
7045	3.2	2.8	10.7	NPH	140.7	5.47	100.9
7046	3.1	2.9	10.2	8.6	139.9	5.72	101.8
7047	3.3	3.1	10.6	NPH	140.8	5.52	100.4
7048	3.3	2.7	10.4	10.0	142.0	5.31	101.7
7049	3.3	2.8	10.1	NPH	141.3	6.28	102.9
7050	3.2	2.9	10.3	9.4	141.4	5.55	102.6

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Olympus Chem Pkg						
	HEM	LIP	ICT	AST (IU/L)	ALT (IU/L)	SDH (IU/L)	ALKP (IU/L)
	22	22	22	22	22	22	22
7061	None	None	None	81	34	7.9	198
7062	Trace	None	None	NPH	32	NPH	188
7063	None	None	None	84	33	7.9	267
7064	None	None	None	77	33	8.6	235
7065	None	None	None	93	32	5.2	181
7066	None	None	None	65	24	8.4	186
7067	Trace	None	None	NPH	25	NPH	222
7068	None	None	None	73	27	10.2	257
7069	None	None	None	77	23	7.3	125
7070	None	None	None	76	33	8.7	196

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Olympus Chem Pkg						
	BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7061	0.12	11	0.21	52	56	105	6.1
7062	0.19	9	0.25	61	45	92	6.3
7063	0.20	11	0.21	71	88	148	6.3
7064	0.19	7	0.19	70	78	150	6.0
7065	0.20	11	0.21	65	54	81	5.8
7066	0.18	12	0.22	73	92	102	6.3
7067	0.18	12	0.22	85	116	101	6.4
7068	0.20	10	0.23	46	47	92	6.3
7069	0.16	11	0.17	62	33	103	5.5
7070	0.17	11	0.18	83	65	91	6.3

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male   Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Olympus Chem Plus						
	ALB (g/dL)	GLOB (g/dL)	CALC (mg/dL)	PHS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
	22	22	22	22	22	22	22
7061	3.2	2.9	10.5	7.8	142.2	4.83	101.7
7062	3.3	2.8	10.3	NPH	142.6	5.41	102.2
7063	3.3	2.8	10.3	8.8	142.1	5.04	100.9
7064	3.3	2.7	10.5	8.9	142.3	5.29	103.6
7065	3.1	2.7	10.8	8.9	140.1	5.27	100.4
7066	3.0	3.1	10.8	8.6	141.9	5.07	101.5
7067	3.3	3.0	10.7	NPH	140.6	5.60	101.6
7068	3.4	2.9	10.7	8.8	141.8	4.87	100.3
7069	3.1	2.4	10.1	8.4	142.2	5.42	104.3
7070	3.2	2.9	10.6	8.4	141.6	4.71	101.3

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Olympus Chem Plus HEM	LIP	ICT	AST (U/L)	ALT (U/L)	SDH (U/L)	ALKP (U/L)
	22	22	22	22	22	22	22
7011	None	None	None	78	33	7.9	152
7012	None	None	None	66	26	5.8	112
7013	None	None	None	78	25	6.7	134
7014	None	None	None	74	21	9.5	112
7015	None	None	None	66	20	7.6	114
7016	None	None	None	59	25	11.0	154
7017	None	None	None	69	23	8.5	131
7018	None	None	None	68	24	8.6	155
7019	Trace	None	None	NPH	27	NPH	140
7020	None	None	None	66	29	13.0	139

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Olympus Chem Plus BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7011	0.18	12	0.29	82	31	116	6.5
7012	0.18	13	0.26	87	31	116	6.7
7013	0.23	12	0.29	85	47	125	6.8
7014	0.16	15	0.29	76	35	150	6.8
7015	0.17	14	0.32	71	41	126	6.3
7016	0.19	11	0.29	90	39	99	6.3
7017	0.15	12	0.25	98	34	105	6.0
7018	0.16	12	0.26	85	32	121	6.5
7019	0.20	12	0.27	102	32	103	6.2
7020	0.19	9	0.24	69	40	118	5.6

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Olympus Chem Plus						
	ALB (g/dL)	GLOB (g/dL)	CALC (mg/dL)	IPHS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
	22	22	22	22	22	22	22
7011	3.6	2.9	10.5	7.3	139.4	4.64	102.0
7012	3.7	3.0	10.7	6.8	140.8	4.35	102.7
7013	3.8	3.0	10.8	7.3	139.4	4.90	103.5
7014	3.7	3.1	10.4	6.6	141.6	4.21	105.2
7015	3.5	2.8	9.9	6.8	139.8	4.14	102.0
7016	3.4	2.9	10.6	7.1	138.5	4.45	101.2
7017	3.3	2.7	10.7	7.9	140.9	5.14	103.8
7018	3.5	3.0	10.8	7.6	141.5	4.63	103.0
7019	3.3	2.9	10.5	NFH	139.6	4.71	102.0
7020	3.3	2.7	10.3	6.6	141.2	4.62	102.6

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Olympus Chem Plus HEM	LIP	ICT	AST (IU/L)	ALT (IU/L)	SDH (U/L)	ALKP (IU/L)
	22	22	22	22	22	22	22
7031	None	None	None	71	34	8.2	97
7032	None	None	None	78	22	8.6	111
7033	None	None	None	78	27	9.2	121
7034	None	None	None	59	26	8.3	115
7035	None	None	None	63	19	9.4	98
7036	None	None	None	58	24	6.3	135
7037	None	None	None	87	32	7.4	102
7038	None	None	None	70	31	8.3	127
7039	Trace	None	None	NFH	20	NFH	90
7040	None	None	None	58	24	6.8	70

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Olympus Chem Plus BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7031	0.20	10	0.24	97	29	91	6.8
7032	0.19	9	0.25	127	47	89	6.9
7033	0.20	11	0.26	73	27	131	7.1
7034	0.21	11	0.26	95	44	105	7.4
7035	0.16	11	0.28	78	30	95	6.4
7036	0.20	12	0.26	91	34	97	6.7
7037	0.20	9	0.22	89	51	95	6.1
7038	0.18	11	0.27	85	42	115	6.4
7039	0.21	10	0.25	137	47	138	6.3
7040	0.19	14	0.28	86	32	166	7.0

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Olympus Chem Plus						
	ALB (g/dL)	GLOB (g/dL)	CALC (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
	22	22	22	22	22	22	22
7031	3.7	3.1	11.1	7.6	140.5	4.28	101.2
7032	3.5	3.4	11.0	8.3	141.0	5.18	99.7
7033	3.9	3.2	11.0	8.4	139.9	4.76	99.6
7034	4.2	3.2	11.2	8.4	140.1	4.78	99.6
7035	3.5	2.9	10.5	7.5	141.8	4.23	103.3
7036	3.7	3.0	11.2	8.3	140.7	4.48	101.2
7037	3.5	2.9	10.6	7.8	140.8	4.68	101.1
7038	3.5	2.9	10.4	7.1	139.9	5.08	102.9
7039	3.5	2.8	11.2	NFH	141.4	4.82	103.6
7040	3.5	3.5	10.8	6.7	140.2	3.92	101.6

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Olympus Chem Plus						
	HEM	LIP	ICT	AST (IU/L)	ALT (IU/L)	SDH (IU/L)	ALKP (IU/L)
	22	22	22	22	22	22	22
7051	None	None	None	73	33	8.2	131
7052	None	None	None	75	36	7.6	152
7053	None	None	None	67	25	8.1	102
7054	None	None	None	56	17	7.6	64
7055	None	None	None	67	29	8.9	113
7056	None	None	None	49	29	6.3	107
7057	None	None	None	60	25	7.9	151
7058	None	None	None	60	28	7.3	106
7059	None	None	None	69	23	9.7	131
7060	None	None	None	66	24	7.8	136

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Olympus Chem Plus						
	BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7051	0.21	13	0.27	96	52	98	6.5
7052	0.19	15	0.25	71	21	97	6.8
7053	0.17	16	0.26	136	50	98	7.3
7054	0.19	12	0.33	108	43	107	6.8
7055	0.20	11	0.26	82	66	127	6.9
7056	0.25	14	0.27	90	41	115	6.6
7057	0.20	13	0.27	106	38	101	6.4
7058	0.20	10	0.28	117	72	96	7.2
7059	0.17	12	0.28	161	57	98	6.6
7060	0.20	11	0.21	125	42	103	6.6

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Clinical Chem Plus						
	ALB	GLOB	CALC	PHOS	NA	K	CL
	(g/dL)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)	(mmol/L)
	22	22	22	22	22	22	22
3051	3.6	2.9	10.5	7.4	139.7	4.52	100.3
3052	3.7	3.1	10.7	7.0	140.3	4.50	102.4
3053	3.8	3.5	11.4	7.8	140.8	4.38	100.9
3054	3.6	3.2	11.3	7.7	140.1	4.78	100.7
3055	3.8	3.3	10.8	7.0	140.9	4.78	101.1
3056	3.6	3.0	11.1	8.1	140.0	4.53	100.4
3057	3.5	2.9	10.9	7.5	139.7	4.51	101.2
3058	3.6	3.2	11.5	7.4	140.3	4.69	101.9
3059	3.5	3.3	11.0	8.2	141.7	4.80	103.3
3060	3.6	3.0	11.2	7.6	139.5	5.02	99.7

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Clinical Chem Pks						
	HEM	LIP	ICT	AST (IU/L)	ALT (IU/L)	SDH (IU/L)	ALKP (IU/L)
	22	22	22	22	22	22	22
7071	None	None	None	70	24	7.5	88
7072	None	None	None	69	31	8.7	148
7073	None	None	None	74	38	12.7	78
7074	None	None	None	64	17	8.9	78
7075	None	None	None	61	28	8.2	115
7076	None	None	None	57	24	11.4	94
7077	None	None	None	62	27	8.3	110
7078	None	None	None	56	26	7.5	104
7079	None	None	None	65	27	15.2	149
7080	None	None	None	67	23	10.2	117

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Clinical Chem Pks						
	BILI (mg/dL)	BUN (mg/dL)	CREA (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	GLUC (mg/dL)	TP (g/dL)
	22	22	22	22	22	22	22
7071	0.20	14	0.25	81	29	103	6.4
7072	0.18	12	0.26	79	29	95	6.6
7073	0.20	12	0.32	128	43	136	7.3
7074	0.19	13	0.31	100	41	157	7.2
7075	0.22	13	0.26	130	36	140	6.5
7076	0.20	11	0.25	61	27	103	6.1
7077	0.19	10	0.25	127	52	136	6.6
7078	0.13	13	0.26	89	31	140	6.3
7079	0.22	13	0.31	90	35	130	6.5
7080	0.20	14	0.32	94	31	123	6.5

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Olympus Chem File						
	ALB (g/dL)	GLOB (g/dL)	CALC (mg/dL)	IPHS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
	22	22	22	22	22	22	22
7071	3.6	2.9	10.5	6.9	139.3	5.21	102.8
7072	3.5	3.1	10.5	6.9	138.0	5.18	101.8
7073	4.1	3.2	11.3	7.3	139.9	4.66	101.3
7074	3.9	3.3	10.8	6.3	141.2	4.29	102.9
7075	3.9	3.0	11.3	6.9	140.7	4.37	101.3
7076	3.3	2.8	10.6	7.6	140.3	4.99	103.3
7077	3.6	3.0	11.1	8.0	139.8	5.23	99.8
7078	3.3	3.0	10.9	8.6	142.3	4.61	103.0
7079	3.5	3.0	10.3	5.7	139.7	4.54	102.1
7080	3.6	2.9	10.0	6.5	140.2	4.29	102.8

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	URINALYSIS						
	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLU (mg/dL)
	22	22	22	22	22	22	22
7001	Light	Yellow	Clear	2.4	6.0	1.072	NEGATIVE
7002	Light	Yellow	Hazy	8.2	6.0	1.029	NEGATIVE
7003	Light	Yellow	Clear	9.6	6.5	1.024	NEGATIVE
7004	Light	Yellow	Clear	6.0	6.5	1.027	NEGATIVE
7005	Light	Yellow	Clear	16.8	6.5	1.013	NEGATIVE
7006	Light	Yellow	Clear	7.2	6.5	1.026	NEGATIVE
7007	Light	Yellow	Clear	18.2	7.0	1.016	NEGATIVE
7008	Light	Yellow	Clear	14.0	6.5	1.016	NEGATIVE
7009	Medium	Yellow	Hazy	5.6	6.5	1.013	NEGATIVE
7010	Light	Yellow	Clear	36.0	7.0	1.008	NEGATIVE

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	URINALYSIS				Chemistry Chem Ph
	KET (mg/dL)	UBIL	BLD	URO (EU/dL)	UMTP (mg/dL)
	22	22	22	22	22
7001	TRACE	NEGATIVE	NEGATIVE	1.0	196
7002	TRACE	NEGATIVE	NEGATIVE	0.2	115
7003	15	NEGATIVE	NEGATIVE	0.2	84
7004	15	NEGATIVE	NEGATIVE	0.2	85
7005	NEGATIVE	NEGATIVE	LARGE	0.2	46
7006	15	NEGATIVE	NEGATIVE	0.2	129
7007	NEGATIVE	NEGATIVE	TRACE	0.2	65
7008	TRACE	NEGATIVE	LARGE	0.2	50
7009	15	NEGATIVE	TRACE	0.2	125
7010	NEGATIVE	NEGATIVE	NEGATIVE	0.2	98

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male   Day(s) Relative to Start Date

512 mg/kg/day Group 2	URINALYSIS						
	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLU (mg/dL)
	22	22	22	22	22	22	22
7021	Light	Yellow	Hazy	4.8	6.0	1.042	NEGATIVE
7022	Light	Yellow	Cloudy	9.6	7.0	1.024	NEGATIVE
7023	Light	Yellow	Hazy	6.0	6.5	1.031	NEGATIVE
7024	Light	Yellow	Clear	4.0	6.0	1.052	NEGATIVE
7025	Light	Yellow	Clear	15.4	7.0	1.015	NEGATIVE
7026	Light	Yellow	Clear	29.0	6.5	1.011	NEGATIVE
7027	Light	Yellow	Clear	15.8	6.5	1.017	NEGATIVE
7028	Light	Yellow	Clear	0.1	QNS	QNS	QNS
7029	Light	Yellow	Hazy	26.0	7.0	1.013	NEGATIVE
7030	Light	Yellow	Clear	4.6	6.0	1.040	NEGATIVE

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Urinalysis				Chemical Chem Pl
	KET (mg/dL)	BIL	BLD	URO (EU/dL)	CMTF (mg/dL)
	22	22	22	22	22
7021	TRACE	NEGATIVE	TRACE	0.2	122
7022	TRACE	NEGATIVE	LARGE	0.2	110
7023	15	NEGATIVE	NEGATIVE	0.2	205
7024	NEGATIVE	NEGATIVE	NEGATIVE	0.2	250
7025	NEGATIVE	NEGATIVE	NEGATIVE	0.2	133
7026	NEGATIVE	NEGATIVE	TRACE	0.2	38
7027	TRACE	NEGATIVE	NEGATIVE	0.2	78
7028	QNS	QNS	QNS	QNS	1260
7029	TRACE	NEGATIVE	NEGATIVE	0.2	24
7030	TRACE	NEGATIVE	NEGATIVE	0.2	185

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male   Day(s) Relative to Start Date

1024 mg/kg/day Group 3	uroATLAS QUAL 22	COL 22	CLAR 22	CVOL (mL) 22	pH 22	SG 22	UGLU (mg/dL) 22
7041	Light	Yellow	Clear	24.4	7.0	1.011	NEGATIVE
7042	Light	Yellow	Clear	9.8	6.5	1.024	NEGATIVE
7043	Light	Yellow	Clear	4.2	6.0	1.042	NEGATIVE
7044	Light	Yellow	Clear	19.0	6.5	1.017	NEGATIVE
7045	Light	Yellow	Hazy	22.0	7.0	1.012	NEGATIVE
7046	Light 9	Brown 9	Cloudy 9	3.6 9	6.5 9	1.063 9	NEGATIVE 9
7047	Light	Yellow	Clear	13.0	6.0	1.022	NEGATIVE
7048	Light	Yellow	Hazy	11.0	6.5	1.026	NEGATIVE
7049	Light	Yellow	Clear	7.0	6.5	1.023	NEGATIVE
7050	Light	Yellow	Clear	9.0	7.0	1.024	NEGATIVE

9 FSC Fecal contamination observed |
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Urinalysis Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	uroLAB LAS				Olympus Chem Plu
	KET	UBIL	BLD	URO	UMTP
	(mg/dL)			(EU/dL)	(mg/dL)
	22	22	22	22	22
7041	TRACE	NEGATIVE	TRACE	0.2	34
7042	TRACE	NEGATIVE	NEGATIVE	0.2	61
7043	TRACE	NEGATIVE	SMALL	0.2	230
7044	NEGATIVE	NEGATIVE	SMALL	0.2	103
7045	TRACE	NEGATIVE	MODERATE	0.2	65
7046	15 [1]	SMALL [1]	LARGE [1]	1.0 [1]	290
7047	TRACE	NEGATIVE	NEGATIVE	0.2	159
7048	15	NEGATIVE	MODERATE	0.2	166
7049	TRACE	NEGATIVE	TRACE	0.2	98
7050	TRACE	NEGATIVE	MODERATE	0.2	93

1 (SC Fecal contamination observed.)
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male   Days Relative to Start Date

1536 mg/kg/day Group 4	uvol/ATLAS						
	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLC (mg/dL)
	22	22	22	22	22	22	22
7061	Light	Yellow	Hazy	15.8	6.5	1.020	NEGATIVE
7062	Light	Yellow	Clear	11.8	6.5	1.019	NEGATIVE
7063	Light	Yellow	Clear	10.2	6.5	1.024	NEGATIVE
7064	Light	Yellow	Clear	31.0	7.0	1.011	NEGATIVE
7065	Light	Yellow	Clear	16.0	6.0	1.018	NEGATIVE
7066	Light	Yellow	Hazy	15.4	7.0	1.017	NEGATIVE
7067	Medium P	Yellow P	Cloudy P	9.6 P	7.0 P	1.022 P	NEGATIVE P
7068	Light	Yellow	Clear	12.8	6.5	1.019	NEGATIVE
7069	Light	Yellow	Clear	1.0	6.0	1.076	NEGATIVE
7070	Light	Yellow	Hazy	19.6	7.0	1.015	NEGATIVE

P [SC Fecal contamination observed]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	URINALYSIS				Olympus Chem Pla
	KET (mg/dL)	UBIL	BLD	URO (EU/dL)	UMTP (mg/dL)
	22	22	22	22	22
7061	TRACE	NEGATIVE	SMALL	0.2	77
7062	NEGATIVE	NEGATIVE	NEGATIVE	0.2	83
7063	15	NEGATIVE	NEGATIVE	0.2	120
7064	NEGATIVE	NEGATIVE	MODERATE	0.2	48
7065	NEGATIVE	NEGATIVE	SMALL	0.2	53
7066	NEGATIVE	NEGATIVE	LARGE	0.2	97
7067	15 P	NEGATIVE P	LARGE P	0.2 P	108
7068	TRACE	NEGATIVE	SMALL	0.2	92
7069	NEGATIVE	NEGATIVE	NEGATIVE	0.2	380
7070	TRACE	NEGATIVE	LARGE	0.2	55

[FSC Fecal contamination Observed]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	URINALYSIS						
	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLU (mg/dL)
	22	22	22	22	22	22	22
2011	Light	Yellow	Clear	0.5	6.0	1.100 [1]	NEGATIVE
2012	Light	Yellow	Clear	1.2	6.0	1.039	NEGATIVE
2013	Light	Yellow	Hazy	7.6	6.5	1.025	NEGATIVE
2014	Light	Yellow	Hazy	3.6	7.0	1.038	NEGATIVE
2015	Light	Yellow	Clear	3.8	6.0	1.047	NEGATIVE
2016	Light	Yellow	Clear	18.2	6.5	1.012	NEGATIVE
2017	Light	Yellow	Clear	15.4	6.5	1.010	NEGATIVE
2018	Light	Yellow	Clear	0.9	6.5	1.058	NEGATIVE
2019	Light	Yellow	Clear	15.0	6.0	1.013	NEGATIVE
2020	Medium	Yellow	Cloudy	8.6	7.0	1.025	NEGATIVE

1 (SG) Specific gravity result is >1.100
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Urine ATLAS				Chemistry Chem Pla
	KET (mg/dL)	UBIL	BLD	URO (EU/dL)	UMTP (mg/dL)
	22	22	22	22	22
7011	NEGATIVE	SMALL	NEGATIVE	0.2	127
7012	NEGATIVE	NEGATIVE	NEGATIVE	0.2	34
7013	NEGATIVE	NEGATIVE	TRACE	0.2	35
7014	NEGATIVE	NEGATIVE	SMALL	0.2	37
7015	NEGATIVE	NEGATIVE	NEGATIVE	0.2	47
7016	NEGATIVE	NEGATIVE	NEGATIVE	0.2	11
7017	NEGATIVE	NEGATIVE	NEGATIVE	0.2	9
7018	NEGATIVE	NEGATIVE	LARGE	0.2	69
7019	NEGATIVE	NEGATIVE	NEGATIVE	0.2	22
7020	NEGATIVE	NEGATIVE	MODERATE	0.2	38

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 1: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	uro/ATLAS						
	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLC (mg/dL)
	22	22	22	22	22	22	22
7031	Light	Yellow	Clear	5.8	6.0	1.031	NEGATIVE
7032	Light	Yellow	Hazy	12.4	7.0	1.013	NEGATIVE
7033	Light	Yellow	Clear	1.0	6.0	1.026	NEGATIVE
7034	Light	Yellow	Hazy	7.6	6.5	1.020	NEGATIVE
7035	Light	Yellow	Clear	11.2	6.0	1.011	NEGATIVE
7036	Light	Yellow	Clear	16.8	6.5	1.011	NEGATIVE
7037	Light	Yellow	Clear	2.8	6.0	1.040	NEGATIVE
7038	Medium	Yellow	Hazy	3.6	6.6	1.051	NEGATIVE
7039	Light	Yellow	Clear	4.0	6.0	1.036	NEGATIVE
7040	Light	Yellow	Clear	3.0	5.5	1.062	NEGATIVE

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	URINALYSIS				Urinary Chem Pn
	KET (mg/dL)	BIL	BLD	URO (EU/dL)	CMTP (mg/dL)
	22	22	22	22	22
7031	TRACE	NEGATIVE	NEGATIVE	0.2	35
7032	NEGATIVE	NEGATIVE	MODERATE	0.2	17
7033	NEGATIVE	NEGATIVE	NEGATIVE	0.2	90
7034	NEGATIVE	NEGATIVE	MODERATE	0.2	29
7035	NEGATIVE	NEGATIVE	NEGATIVE	0.2	16
7036	NEGATIVE	NEGATIVE	NEGATIVE	0.2	14
7037	TRACE	SMALL	SMALL	0.2	45
7038	TRACE	SMALL	MODERATE	0.2	63
7039	TRACE	NEGATIVE	NEGATIVE	0.2	41
7040	NEGATIVE	NEGATIVE	MODERATE	0.2	65

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

1023 mg/kg/day Group 3	uvol-ATLAS						
	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLU (mg/dL)
	22	22	22	22	22	22	22
7051	Medium	Yellow	Hazy	3.0	6.0	1.046	NEGATIVE
7052	Light	Yellow	Clear	3.6	6.0	1.043	NEGATIVE
7053	Light	Yellow	Cloudy	8.0	7.0	1.021	NEGATIVE
7054	Light	Yellow	Clear	10.8	6.0	1.017	NEGATIVE
7055	Light	Yellow	Clear	3.0	6.5	1.040	NEGATIVE
7056	Light	Yellow	Clear	10.2	6.5	1.020	NEGATIVE
7057	Medium 0	Brown 0	Turbid 0	1.0 0	7.5 0	1.028 0	NEGATIVE 0
7058	Medium	Yellow	Cloudy	7.0	7.0	1.022	NEGATIVE
7059	Light 0	Brown 0	Cloudy 0	9.6 0	7.5 0	1.017 0	NEGATIVE 0
7060	Light	Yellow	Clear	6.2	6.0	1.027	NEGATIVE

[0SC Fecal contamination observed]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1023 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1534 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	uvol-ATLAS				Clinical Chem Pla
	KET (mg/dL)	UBIL	BLD	URO (EU/dL)	UMTP (mg/dL)
	22	22	22	22	22
7051	TRACE	SMALL	LARGE	0.2	43
7052	NEGATIVE	NEGATIVE	NEGATIVE	0.2	11
7053	TRACE	NEGATIVE	LARGE	0.2	31
7054	NEGATIVE	NEGATIVE	NEGATIVE	0.2	15
7055	NEGATIVE	NEGATIVE	NEGATIVE	0.2	40
7056	NEGATIVE	NEGATIVE	NEGATIVE	0.2	20
7057	TRACE P	SMALL P	LARGE P	0.2 P	56
7058	NEGATIVE	NEGATIVE	LARGE	0.2	32
7059	NEGATIVE P	NEGATIVE P	LARGE P	0.2 P	35
7060	NEGATIVE	NEGATIVE	LARGE	0.2	30

P (USC Fecal contamination observed.)
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation - A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	QUAL	COL	CLAR	UVOL (mL)	pH	SG	UGLU (mg/dL)
	22	22	22	22	22	22	22
2071	Light I	Brown I	Cloudy I	7.8 I	7.0 I	1.024 I	NEGATIVE I
2072	Light	Yellow	Clear	7.8	6.0	1.022	NEGATIVE
2073	Light	Yellow	Clear	5.0	6.0	1.026	NEGATIVE
2074	Light	Yellow	Clear	2.6	6.0	1.046	NEGATIVE
2075	Light	Yellow	Clear	12.8	6.0	1.015	NEGATIVE
2076	Light	Yellow	Clear	3.0	6.0	1.056	NEGATIVE
2077	Medium	Yellow	Hazy	7.0	6.5	1.027	NEGATIVE
2078	Light	Yellow	Clear	14.0	6.5	1.014	NEGATIVE
2079	Dark I	Brown I	Turbid I	4.0 I	8.0 I	1.031 I	NEGATIVE I
2080	Light	Yellow	Clear	2.2	6.5	1.039	NEGATIVE

I [SC Fecal contamination observed]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	[illegible] ATLAS				Olympus Chem Plu
	KET (mg/dL)	UBIL	BLD	URO (EU/dL)	UMTP (mg/dL)
	22	22	22	22	22
7071	NEGATIVE F	NEGATIVE F	LARGE F	0.2 F	47
7072	NEGATIVE	NEGATIVE	SMALL	0.2	23
7073	NEGATIVE	NEGATIVE	TRACE	0.2	42
7074	NEGATIVE	NEGATIVE	MODERATE	0.2	49
7075	NEGATIVE	NEGATIVE	SMALL	0.2	15
7076	NEGATIVE	NEGATIVE	NEGATIVE	0.2	59
7077	NEGATIVE	NEGATIVE	LARGE	0.2	38
7078	NEGATIVE	NEGATIVE	LARGE	0.2	15
7079	TRACE F	MODERATE F	LARGE F	1.0 F	118
7080	NEGATIVE	NEGATIVE	MODERATE	0.2	38

1 [SC Fecal contamination observed]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1023 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	SCRY (/hpf)	MICR (/hpf)	SPER (/lpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7001	Few I	- I	- I	Few I	Few I	Mod I	- I	- I
7002	Few	Few	-	Few	Mod	Mod	-	Few
7003	Few	-	-	Few	Few	Mod	-	-
7004	Few		-	Few	Few	Few	-	-
7005	Few	-	-	Few	Mod	Few	-	-
7006	Few	.	.	Mod	Mod	Mod		
7007	-	-	-	Few	Few	Few	-	-
7008	.	.	-	-	Few	Few	-	-
7009	Few	Few	.	Mod	Mod	Mod		.
7010	Few	-	-	Few	Few	Few	-	-

I [SC urine below recommended volume]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male   Day(s) Relative to Start Date

512 mg/kg/day Group 2	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/lpf)	REPI (/lpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7021	Few	-	-	Few	Few	Few	.	
7022	Few	Few	-	Mod	Mod	Mod	-	-
7023	Few	Few	-	Few	Few	Man	.	-
7024		.	-	Few	Few	Few	.	.
7025	Few	-	-	Few	Few	Few	-	-
7026	.	.	-	Few	Few	Few		.
7027	Few	Few	-	Few	Mod	Few	-	-
7028	QNS							
7029	Few	.	-	Few	Few	Few		
7030	Few	-	-	Few	Few	Few	-	-

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/hpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7041	Few	-	-	Few	Few	Few	-	-
7042	Few	-	-	-	Few	Few	-	-
7043	Few	Few	-	Few	Few	Few	-	-
7044	Few	Few		Few	Mod	Mod	-	-
7045	Few	Few	-	Mod	Mod	Mod	-	-
7046	Few	Few	-	Man	Mod	Mod		-
7047	-	-	-	-	Few	Few	-	-
7048	Few	Few	-	Mod	Mod	Mod	-	-
7049	Few	-	-	Few	Few	Few	-	-
7050	Few	-	-	Few	Few	Few	-	-

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/lpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7061	-	-	-	-	Few	Few	-	-
7062	Few	-	-	Few	Few	Few	-	-
7063	Few	-	-	Few	Few	Few	-	-
7064	Few			Few	Mod	Few	-	-
7065	Few	Few	-	Few	Few	Mod	Few	-
7066	Few	-	-	Few	Few	Few	-	-
7067	Few	-	-	Mod	Mod	Mod	-	-
7068	-	-	-	-	Few	Few	-	-
7069	Few [1]	Few [1]	- [1]	Few [1]	Mod [1]	Mod [1]	[1]	[1]
7070	Few	Few	-	Few	Few	Few	-	-

[1] USC urine below recommended volume
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female   Day(s) Relative to Start Date

mg/kg/day (Group 1)	Urine Microscopic EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/lpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7011	Few	Few	-	Few	Mod	-	-	-
7012	Few	-	-	Few	Few	-	Few	
7013	Few	Few	-	Mod	Mod	-	-	-
7014	Few	Few	-	Mod	Mod	-	-	-
7015	Few	Few	-	-	Few	-	-	-
7016	Few	-	-	Few	Few	-	-	-
7017	Few		-	-	Few	-	-	
7018	Few I	I	- I	Few I	Few I	- I	- I	- I
7019	Few	-	-	Few	Few	-	-	-
7020	Few	Few	-	Few	Mod	-	-	-

I [ISC urine below recommended volume]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/hpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7031	Few	Few	-	Few	Few	-	-	-
7032	Few	-	-	Mod	Mod	-		
7033	Few	Few	-	Few	Few	-	-	-
7034	-	-	-	Few	Mod	-	-	-
7035	Few	Few	-	Few	Mod	-	-	-
7036	-	-	-	Few	Few	-	-	-
7037	Few I	Few I	- I	Few I	Mod I	- I	I	- I
7038	Few	-	-	Mod	Mod	-	-	-
7039	-	-	-	Few	Few	-	-	-
7040	Few	-	-	Few	Few	-	-	-

I [SC urine below recommended volume]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/lpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7051	Few	Few	-	Few	Mod	-	-	-
7052	Few		-	Few	Mod	-		
7053	Few	Few	-	Mod	Mod	-	-	-
7054	Few	Few	-	Mod	Mod	-	-	-
7055	Few	Few	-	Few	Few	-	-	-
7056	Few	-	-	Few	Few	-	-	-
7057	Few	Few	Few	Man	Man	-		
7058	Few	Few	Few	Mod	Man	-	-	-
7059	Few	Few	Few	Man	Man	-	-	-
7060	Few	-	-	Mod	Mod	-	-	-

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Urine Microscopic							
	EPIT (/hpf)	UWBC (/hpf)	URBC (/hpf)	NCRY (/hpf)	MICR (/hpf)	SPER (/lpf)	REPI (/hpf)	MUC (/lpf)
	22	22	22	22	22	22	22	22
7071	Few	Few	-	Man	Man	-	-	Few
7072	Few		-	Few	Few	-		
7073	Few	-	-	Few	Few	-	-	-
7074	Few [1]	- [1]	- [1]	Few [1]	Mod [1]	- [1]	- [1]	- [1]
7075	Few	Few	-	Few	Few	-	-	-
7076	Few	-	-	Few	Few	-	-	-
7077	Few	-	-	Few	Mod	-		
7078	Few		-	Few	Few	-	-	
7079	Few	Few	Few	Mod	Man	-	-	-
7080	Few	-	-	Few	Few	-	-	-

[1] SC urine below recommended volume

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

APPENDIX O: ANIMAL NUMBERS, DOSE GROUPS, AND FATES[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Fates

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
1	0 mg/kg/day	Male	7001	1	29	4	27/10/16	6:50	.	Term	Term
			7002	1	29	4	27/10/16	6:51	.	Term	Term
			7003	2	29	4	27/10/16	6:51	.	Term	Term
			7004	2	29	4	27/10/16	6:51	.	Term	Term
			7005	3	29	4	27/10/16	6:52	.	Term	Term
			7006	3	29	4	27/10/16	6:52	.	Term	Term
			7007	4	29	4	27/10/16	6:52	.	Term	Term
			7008	4	29	4	27/10/16	6:53	.	Term	Term
			7009	5	29	4	27/10/16	6:53	.	Term	Term
			7010	5	29	4	27/10/16	6:53	.	Term	Term
1	0 mg/kg/day	Female	7011	6	30	4	28/10/16	6:50	.	Term	Term
			7012	6	30	4	28/10/16	6:50	.	Term	Term
			7013	7	30	4	28/10/16	6:50	.	Term	Term
			7014	7	30	4	28/10/16	6:51	.	Term	Term
			7015	8	30	4	28/10/16	6:51	.	Term	Term
			7016	8	30	4	28/10/16	6:51	.	Term	Term
			7017	9	30	4	28/10/16	6:52	.	Term	Term
			7018	9	30	4	28/10/16	6:52	.	Term	Term
			7019	10	30	4	28/10/16	6:53	.	Term	Term
			7020	10	30	4	28/10/16	6:53	.	Term	Term
2	512 mg/kg/day	Male	7021	11	29	4	27/10/16	6:56	.	Term	Term
			7022	11	29	4	27/10/16	6:57	.	Term	Term
			7023	12	29	4	27/10/16	6:57	.	Term	Term
			7024	12	29	4	27/10/16	6:57	.	Term	Term
			7025	13	29	4	27/10/16	6:58	.	Term	Term
			7026	13	29	4	27/10/16	6:58	.	Term	Term
			7027	14	29	4	27/10/16	6:59	.	Term	Term
			7028	14	29	4	27/10/16	6:59	.	Term	Term
			7029	15	29	4	27/10/16	6:59	.	Term	Term

Individual Animal Fates

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	512 mg/kg/day	Male	7030	15	29	4	27/10/16	7:00	.	Term	Term
2	512 mg/kg/day	Female	7031	16	30	4	28/10/16	6:54	.	Term	Term
			7032	16	30	4	28/10/16	6:54	.	Term	Term
			7033	17	30	4	28/10/16	6:55	.	Term	Term
			7034	17	30	4	28/10/16	6:55	.	Term	Term
			7035	18	30	4	28/10/16	6:55	.	Term	Term
			7036	18	30	4	28/10/16	6:56	.	Term	Term
			7037	19	30	4	28/10/16	6:56	.	Term	Term
			7038	19	30	4	28/10/16	6:56	.	Term	Term
			7039	20	30	4	28/10/16	6:57	.	Term	Term
			7040	20	30	4	28/10/16	6:57	.	Term	Term
3	1024 mg/kg/day	Male	7041	21	29	4	27/10/16	7:00	.	Term	Term
			7042	21	29	4	27/10/16	7:00	.	Term	Term
			7043	22	29	4	27/10/16	7:01	.	Term	Term
			7044	22	29	4	27/10/16	7:01	.	Term	Term
			7045	23	29	4	27/10/16	7:02	.	Term	Term
			7046	23	29	4	27/10/16	7:02	.	Term	Term
			7047	24	29	4	27/10/16	7:03	.	Term	Term
			7048	24	29	4	27/10/16	7:03	.	Term	Term
			7049	25	29	4	27/10/16	7:04	.	Term	Term
			7050	25	29	4	27/10/16	7:04	.	Term	Term
3	1024 mg/kg/day	Female	7051	26	30	4	28/10/16	6:58	.	Term	Term
			7052	26	30	4	28/10/16	6:58	.	Term	Term
			7053	27	30	4	28/10/16	6:58	.	Term	Term
			7054	27	30	4	28/10/16	6:59	.	Term	Term
			7055	28	30	4	28/10/16	6:59	.	Term	Term
			7056	28	30	4	28/10/16	6:59	.	Term	Term
			7057	29	30	4	28/10/16	6:59	.	Term	Term

Individual Animal Fates

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	1024 mg/kg/day	Female	7058	29	30	4	28/10/16	7:00	.	Term	Term
			7059	30	30	4	28/10/16	7:00	.	Term	Term
			7060	30	30	4	28/10/16	7:01	.	Term	Term
4	1536 mg/kg/day	Male	7061	31	29	4	27/10/16	7:05	.	Term	Term
			7062	31	29	4	27/10/16	7:05	.	Term	Term
			7063	32	29	4	27/10/16	7:05	.	Term	Term
			7064	32	29	4	27/10/16	7:06	.	Term	Term
			7065	33	29	4	27/10/16	7:06	.	Term	Term
			7066	33	29	4	27/10/16	7:06	.	Term	Term
			7067	34	29	4	27/10/16	7:07	.	Term	Term
			7068	34	29	4	27/10/16	7:07	.	Term	Term
			7069	35	29	4	27/10/16	7:07	.	Term	Term
			7070	35	29	4	27/10/16	7:08	.	Term	Term
4	1536 mg/kg/day	Female	7071	36	30	4	28/10/16	7:01	.	Term	Term
			7072	36	30	4	28/10/16	7:01	.	Term	Term
			7073	37	30	4	28/10/16	7:02	.	Term	Term
			7074	37	30	4	28/10/16	7:02	.	Term	Term
			7075	38	30	4	28/10/16	7:02	.	Term	Term
			7076	38	30	4	28/10/16	7:03	.	Term	Term
			7077	39	30	4	28/10/16	7:03	.	Term	Term
			7078	39	30	4	28/10/16	7:03	.	Term	Term
			7079	40	30	4	28/10/16	7:04	.	Term	Term
			7080	40	30	4	28/10/16	7:04	.	Term	Term

APPENDIX P: INDIVIDUAL ANIMAL NECROPSY OBSERVATIONS[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Animal: 7001 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7002 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

testes-combined : size: 1 x 1.5 cm
testes-combined : right; small; soft
epididymides-combined : size: 3 x 0.5 cm
epididymides-combined : right; small

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7003 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7004 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7005 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7006 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7007	Group:	1	Sex:	Male
		Dose:	0		
Necropsy Date:	10/27/2016				

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7008	Group:	1	Sex:	Male
		Dose:	0		
Necropsy Date:	10/27/2016				

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7009	Group:	1	Sex:	Male
		Dose:	0		
Necropsy Date:	10/27/2016				

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7010	Group:	1	Sex:	Male
		Dose:	0		
Necropsy Date:	10/27/2016				

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7011	Group:	1	Sex:	Female
		Dose:	0		
Necropsy Date:	10/28/2016				

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7012	Group:	1	Sex:	Female
		Dose:	0		
Necropsy Date:	10/28/2016				

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7013 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7014 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7015 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7016 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7017 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7018 Group: 1 Sex: Female
Dose: 0

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7019 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7020 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7021 Group: 2 Sex: Male
Dose: 512
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7022 Group: 2 Sex: Male
Dose: 512
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7023 Group: 2 Sex: Male
Dose: 512
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7024 Group: 2 Sex: Male

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Dose: 512

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7025 Group: 2 Sex: Male

Dose: 512

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7026 Group: 2 Sex: Male

Dose: 512

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7027 Group: 2 Sex: Male

Dose: 512

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7028 Group: 2 Sex: Male

Dose: 512

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7029 Group: 2 Sex: Male

Dose: 512

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Animal: 7030 Group: 2 Sex: Male
Dose: 512
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7031 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7032 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7033 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7034 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7035 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Last Clinical Observations:

Alopecia, Left Forelimb, Moderate
Alopecia, Right Forelimb, Moderate

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

non correlated finding : no correlated finding [Alopecia, Left Forelimb, Moderate (C) | Alopecia, Right Forelimb, Moderate (C)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7036 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7037 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7038 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7039 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7040 Group: 2 Sex: Female
Dose: 512
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7041 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7042 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7043 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7044 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7045 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7046 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7047 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

brain : focal depressed area on left hemisphere. Possible prosection damage

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7048 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7049 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7050 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7051 Group: 3 Sex: Female
Dose: 1024
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7052 Group: 3 Sex: Female
Dose: 1024
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7053 Group: 3 Sex: Female
Dose: 1024

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7054	Group:	3	Sex:	Female
		Dose:	1024		

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7055	Group:	3	Sex:	Female
		Dose:	1024		

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

spleen : stricture

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7056	Group:	3	Sex:	Female
		Dose:	1024		

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7057	Group:	3	Sex:	Female
		Dose:	1024		

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7058	Group:	3	Sex:	Female
		Dose:	1024		

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7059	Group:	3	Sex:	Female

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Dose: 1024

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7060 Group: 3 Sex: Female
Dose: 1024

Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7061 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7062 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7063 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7064 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Animal: 7065 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7066 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7067 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7068 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7069 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Last Clinical Observations:

Eschar, Head, Superficial

Gross Pathology Observations [Correlation]:

non correlated finding : no correlated finding [Eschar, Head, Superficial (C)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7070 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7071 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7072 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7073 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7074 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7075 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7076 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7077	Group: 4		Sex: Female
	Dose: 1536		
Necropsy Date: 10/28/2016			

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7078	Group: 4		Sex: Female
	Dose: 1536		
Necropsy Date: 10/28/2016			

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7079	Group: 4		Sex: Female
	Dose: 1536		
Necropsy Date: 10/28/2016			

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7080	Group: 4		Sex: Female
	Dose: 1536		
Necropsy Date: 10/28/2016			

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

APPENDIX Q: INDIVIDUAL ANIMAL TERMINAL BODY AND ORGAN WEIGHTS[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

0 mg/kg/day Group 1	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Epididymides Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)
	--	--	--	--	--	--	--
7001	399	0.073	2.19	1.14	1.31	3.19	11.08
7002	359	0.071	2.16	0.94	1.13	2.81	14.06
7003	376	0.071	2.15	0.94	1.19	2.66	12.53
7004	337	0.056	1.98	0.82	1.06	2.26	11.00
7005	329	0.063	2.10	1.04	1.07	2.20	8.44
7006	401	0.066	2.20	1.20	1.30	2.54	11.90
7007	395	0.068	2.13	1.17	1.35	2.83	11.68
7008	355	0.071	2.21	1.04	1.18	2.59	9.44
7009	370	0.062	2.00	0.93	1.11	2.47	9.76
7010	354	0.053	2.29	1.10	1.25	2.86	12.29
Mean	367.5	0.0654	2.141	1.032	1.195	2.641	11.218
SD	25.3	0.0068	0.095	0.123	0.104	0.297	1.657
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

0 mg/kg/day Group 1	Spleen Wt (g)	Testes Wt (g)	Thymus Wt (g)
	--	--	--
7001	0.86	3.65	0.845
7002	0.78	2.18	0.583
7003	0.85	3.27	0.495
7004	0.72	2.43	0.385
7005	0.76	2.91	0.633
7006	0.98	3.12	0.397
7007	1.05	3.96	0.659
7008	0.91	3.34	0.414
7009	0.77	3.23	0.474
7010	0.63	3.39	0.320
Mean	0.831	3.148	0.5205
SD	0.125	0.531	0.1595
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Epididymides Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)
	--	--	--	--	--	--	--
7021	363	0.076	1.96	1.17	1.14	2.68	11.05
7022	374	0.074	2.21	1.10	1.28	3.01	11.54
7023	386	0.054	2.22	1.19	1.29	2.47	10.80
7024	374	0.067	2.31	1.08	1.28	2.57	10.74
7025	362	0.069	2.09	1.05	1.12	2.42	10.75
7026	378	0.053	2.17	1.17	1.26	2.86	12.25
7027	366	0.087	2.15	1.01	1.28	2.65	10.57
7028	336	0.058	2.14	1.06	1.13	2.67	10.68
7029	428	0.062	2.21	0.92	1.54	3.01	12.52
7030	358	0.055	1.97	1.13	1.22	2.44	10.92
Mean	372.5	0.0655	2.143	1.088	1.254	2.678	11.182
SD	23.8	0.0112	0.110	0.083	0.121	0.219	0.691
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Spleen Wt (g)	Testes Wt (g)	Thymus Wt (g)
	--	--	--
7021	0.80	3.39	0.359
7022	0.84	3.09	0.623
7023	0.78	2.95	0.521
7024	0.73	3.39	0.639
7025	0.86	3.16	0.406
7026	0.92	3.96	0.648
7027	0.68	3.42	0.715
7028	1.04	3.63	0.614
7029	0.72	3.56	0.643
7030	0.76	3.26	0.493
Mean	0.813	3.381	0.5661
SD	0.107	0.292	0.1162
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Epididymides Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)
	--	--	--	--	--	--	--
7041	375	0.068	2.20	1.14	1.15	2.89	13.47
7042	421	0.074	2.29	1.07	1.38	2.91	13.21
7043	355	0.056	2.14	0.93	1.21	2.50	10.42
7044	406	0.067	2.33	1.35	1.36	2.96	13.78
7045	377	0.064	2.25	0.94	1.27	2.45	11.88
7046	418	0.060	2.27	0.96	1.46	3.11	13.24
7047	404	0.046	1.87	0.98	1.30	2.79	12.54
7048	413	0.066	2.31	1.06	1.32	3.10	15.05
7049	328	0.035	2.12	0.93	1.13	2.51	9.59
7050	343	0.057	2.08	0.99	1.14	2.67	9.99
Mean	384.0	0.0593	2.186	1.035	1.272	2.789	12.317
SD	33.4	0.0116	0.140	0.131	0.113	0.246	1.804
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Spleen Wt (g)	Testes Wt (g)	Thymus Wt (g)
	--	--	--
7041	0.82	3.57	0.513
7042	0.78	2.99	0.534
7043	0.77	3.43	0.441
7044	0.75	3.76	0.502
7045	0.68	3.30	0.559
7046	0.82	3.15	0.841
7047	0.83	3.12	0.552
7048	0.78	3.18	0.612
7049	0.78	3.16	0.409
7050	0.68	3.00	0.503
Mean	0.769	3.266	0.5466
SD	0.053	0.251	0.1185
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Epididymides Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)
	--	--	--	--	--	--	--
7061	381	0.064	2.09	1.04	1.22	2.61	10.92
7062	379	0.058	2.14	0.88	1.26	2.83	10.89
7063	353	0.063	1.99	1.13	1.08	2.78	12.40
7064	413	0.064	2.27	0.87	1.29	3.05	12.47
7065	405	0.075	2.24	0.91	1.36	3.21	13.51
7066	394	0.069	2.15	1.10	1.29	2.77	14.23
7067	389	0.073	2.10	1.05	1.13	2.48	11.20
7068	361	0.084	2.22	1.12	1.20	2.77	12.87
7069	350	0.049	2.02	0.94	1.12	2.48	9.43
7070	368	0.073	2.30	1.04	1.24	3.02	13.01
Mean	379.3	0.0672	2.152	1.008	1.219	2.800	12.093
SD	21.4	0.0098	0.105	0.100	0.088	0.241	1.452
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Spleen Wt (g)	Testes Wt (g)	Thymus Wt (g)
	--	--	--
7061	0.82	3.22	0.476
7062	0.77	3.00	0.366
7063	0.87	3.25	0.510
7064	0.86	3.66	0.437
7065	0.82	3.25	0.715
7066	0.75	3.00	0.548
7067	0.73	2.99	0.549
7068	1.01	3.56	0.702
7069	0.61	3.55	0.461
7070	0.85	3.24	0.512
Mean	0.809	3.272	0.5276
SD	0.105	0.246	0.1097
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Ovaries with Oviducts Wt (g)
	-	-	-	-	-	-	-
7011	194	0.061	1.83	0.73	1.59	6.61	0.124
7012	206	0.075	1.94	0.74	1.68	6.20	0.128
7013	266	0.084	2.14	1.00	2.07	7.83	0.152
7014	227	0.076	2.09	0.90	1.83	6.79	0.145
7015	236	0.069	2.08	0.90	1.65	7.32	0.139
7016	227	0.068	1.94	0.83	1.68	8.19	0.124
7017	205	0.067	1.94	0.71	1.50	6.05	0.104
7018	241	0.070	2.02	0.91	1.85	7.23	0.156
7019	240	0.079	2.05	0.85	1.86	7.74	0.108
7020	250	0.068	2.04	0.83	1.81	7.60	0.129
Mean	229.2	0.0717	2.007	0.840	1.752	7.156	0.1309
SD	22.3	0.0067	0.093	0.092	0.164	0.720	0.0173
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Spleen Wt (g)	Thymus Wt (g)	Uterus Wt (g)
	-	-	-
7011	0.39	0.369	0.57
7012	0.42	0.258	0.60
7013	0.60	0.480	0.96
7014	0.49	0.460	0.65
7015	0.42	0.491	0.56
7016	0.56	0.481	0.48
7017	0.47	0.385	0.87
7018	0.53	0.373	0.97
7019	0.66	0.413	0.44
7020	0.44	0.633	1.17
Mean	0.498	0.4343	0.727
SD	0.088	0.0998	0.247
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Ovaries with Oviducts Wt (g)
	-	-	-	-	-	-	-
7031	234	0.072	2.02	0.88	1.88	7.87	0.118
7032	216	0.074	2.05	0.80	1.91	7.42	0.119
7033	217	0.085	2.01	0.79	1.95	7.54	0.141
7034	199	0.061	1.92	0.75	1.61	6.34	0.113
7035	233	0.068	1.92	0.85	1.61	7.63	0.142
7036	228	0.063	1.86	0.82	1.76	8.83	0.129
7037	182	0.059	1.88	0.75	1.57	5.93	0.096
7038	247	0.083	1.88	0.87	1.83	7.05	0.133
7039	243	0.070	2.16	0.87	2.00	8.62	0.124
7040	257	0.078	2.06	0.92	2.08	9.13	0.157
Mean	225.6	0.0713	1.976	0.830	1.820	7.636	0.1272
SD	22.7	0.0089	0.099	0.057	0.177	1.037	0.0172
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

512 mg/kg/day Group 2	Spleen Wt (g)	Thymus Wt (g)	Uterus Wt (g)
	-	-	-
7031	0.61	0.473	0.46
7032	0.43	0.446	0.54
7033	0.54	0.532	0.54
7034	0.39	0.492	0.41
7035	0.43	0.411	0.38
7036	0.60	0.480	0.43
7037	0.39	0.370	0.54
7038	0.44	0.625	0.45
7039	0.61	0.396	0.41
7040	0.74	0.429	0.41
Mean	0.518	0.4654	0.457
SD	0.119	0.0741	0.061
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Ovaries with Oviducts Wt (g)
	-	-	-	-	-	-	-
7051	217	0.056	2.14	0.82	1.71	7.05	0.134
7052	227	0.067	1.94	0.83	1.81	8.34	0.108
7053	247	0.061	2.07	0.85	1.62	7.54	0.116
7054	246	0.077	2.01	0.86	1.52	7.11	0.122
7055	257	0.065	2.03	0.92	1.98	7.85	0.140
7056	250	0.066	2.11	0.81	1.81	7.24	0.107
7057	222	0.051	1.97	0.82	1.75	7.31	0.134
7058	224	0.065	2.07	0.86	1.70	6.82	0.105
7059	248	0.077	1.96	0.89	1.94	6.57	0.144
7060	225	0.079	2.16	0.84	1.85	7.55	0.121
Mean	236.3	0.0664	2.046	0.850	1.769	7.338	0.1231
SD	14.5	0.0092	0.077	0.034	0.140	0.512	0.0143
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Spleen Wt (g)	Thymus Wt (g)	Uterus Wt (g)
	-	-	-
7051	0.55	0.395	0.46
7052	0.48	0.581	0.43
7053	0.53	0.445	1.29
7054	0.51	0.339	0.54
7055	0.48	0.534	0.63
7056	0.62	0.635	0.45
7057	0.56	0.531	0.49
7058	0.45	0.363	0.43
7059	0.52	0.435	0.90
7060	0.37	0.504	0.53
Mean	0.507	0.4762	0.615
SD	0.068	0.0967	0.276
N	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Ovaries with Oviducts Wt (g)
	-	-	-	-	-	-	-
7071	235	0.065	2.03	0.81	1.77	8.18	0.144
7072	232	0.074	2.02	0.85	1.87	7.67	0.142
7073	244	0.073	1.94	0.91	1.72	7.76	0.140
7074	221	0.064	2.08	0.78	1.90	7.15	0.105
7075	225	0.077	2.05	0.81	1.80	8.84	0.145
7076	234	0.080	2.02	0.82	2.02	8.32	0.145
7077	255	0.064	2.05	0.89	1.87	7.75	0.126
7078	222	0.082	1.93	0.83	1.79	7.09	0.129
7079	248	0.092	2.04	0.99	1.70	7.39	0.160
7080	222	0.066	2.05	0.79	1.71	7.48	0.128
Mean	233.8	0.0737	2.021	0.848	1.815	7.763	0.1364
SD	11.9	0.0093	0.049	0.065	0.101	0.548	0.0150
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Spleen Wt (g)	Thymus Wt (g)	Uterus Wt (g)
	-	-	-
7071	0.60	0.643	0.46
7072	0.54	0.459	0.52
7073	0.51	0.379	0.52
7074	0.39	0.379	0.52
7075	0.48	0.440	0.50
7076	0.53	0.665	0.49
7077	0.54	0.616	0.38
7078	0.49	0.584	0.41
7079	0.58	0.440	0.56
7080	0.47	0.613	0.54
Mean	0.513	0.5218	0.490
SD	0.060	0.1127	0.057
N	10	10	10

APPENDIX R: INDIVIDUAL ANIMAL ORGAN-TO-BODY WEIGHT RATIOS[1]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Epididymides /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7001	0.183	5.49	2.857	3.28	7.99	27.77	2.16
7002	0.198	6.02	2.618	3.15	7.83	39.16	2.17
7003	0.189	5.72	2.500	3.16	7.07	33.32	2.26
7004	0.166	5.88	2.433	3.15	6.71	32.64	2.14
7005	0.191	6.38	3.161	3.25	6.69	25.65	2.31
7006	0.165	5.49	2.993	3.24	6.33	29.68	2.44
7007	0.172	5.39	2.962	3.42	7.16	29.57	2.66
7008	0.200	6.23	2.930	3.32	7.30	26.59	2.56
7009	0.168	5.41	2.514	3.00	6.68	26.38	2.08
7010	0.150	6.47	3.107	3.53	8.08	34.72	1.78
Mean	0.1781	5.846	2.8075	3.251	7.184	30.549	2.256
SD	0.0165	0.411	0.2682	0.151	0.610	4.348	0.255
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	Testes /TBW (Ratio)	Thymus /TBW (Ratio)
	-	-
7001	9.15	2.118
7002	6.07	1.624
7003	8.70	1.316
7004	7.21	1.142
7005	8.84	1.924
7006	7.78	0.990
7007	10.03	1.668
7008	9.41	1.166
7009	8.73	1.281
7010	9.58	0.904
Mean	8.549	1.4134
SD	1.201	0.4037
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Epididymides /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7021	0.209	5.40	3.223	3.14	7.38	30.44	2.20
7022	0.198	5.91	2.941	3.42	8.05	30.86	2.25
7023	0.140	5.75	3.083	3.34	6.40	27.98	2.02
7024	0.179	6.18	2.888	3.42	6.87	28.72	1.95
7025	0.191	5.77	2.901	3.09	6.69	29.70	2.38
7026	0.140	5.74	3.095	3.33	7.57	32.41	2.43
7027	0.238	5.87	2.760	3.50	7.24	28.88	1.86
7028	0.173	6.37	3.155	3.36	7.95	31.79	3.10
7029	0.145	5.16	2.150	3.60	7.03	29.25	1.68
7030	0.154	5.50	3.156	3.41	6.82	30.50	2.12
Mean	0.1766	5.766	2.9351	3.362	7.199	30.052	2.199
SD	0.0328	0.355	0.3125	0.151	0.541	1.405	0.391
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Testes /TBW (Ratio)	Thymus /TBW (Ratio)
	-	-
7021	9.34	0.989
7022	8.26	1.666
7023	7.64	1.350
7024	9.06	1.709
7025	8.73	1.122
7026	10.48	1.714
7027	9.34	1.954
7028	10.80	1.827
7029	8.32	1.502
7030	9.11	1.377
Mean	9.108	1.5209
SD	0.971	0.3105
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Epididymides /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7041	0.181	5.87	3.040	3.07	7.71	35.92	2.19
7042	0.176	5.44	2.542	3.28	6.91	31.38	1.85
7043	0.158	6.03	2.620	3.41	7.04	29.35	2.17
7044	0.165	5.74	3.325	3.35	7.29	33.94	1.85
7045	0.170	5.97	2.493	3.37	6.50	31.51	1.80
7046	0.144	5.43	2.297	3.49	7.44	31.67	1.96
7047	0.114	4.63	2.426	3.22	6.91	31.04	2.05
7048	0.160	5.59	2.567	3.20	7.51	36.44	1.89
7049	0.107	6.46	2.835	3.45	7.65	29.24	2.38
7050	0.166	6.06	2.886	3.32	7.78	29.13	1.98
Mean	0.1540	5.722	2.7030	3.315	7.274	31.962	2.012
SD	0.0253	0.497	0.3143	0.128	0.421	2.654	0.184
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male   Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Testes /TBW (Ratio)	Thymus /TBW (Ratio)
	-	-
7041	9.52	1.368
7042	7.10	1.268
7043	9.66	1.242
7044	9.26	1.236
7045	8.75	1.483
7046	7.54	2.012
7047	7.72	1.366
7048	7.70	1.482
7049	9.63	1.247
7050	8.75	1.466
Mean	8.564	1.4171
SD	0.970	0.2319
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Epididymides /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7061	0.168	5.49	2.730	3.20	6.85	28.66	2.15
7062	0.153	5.65	2.322	3.32	7.47	28.73	2.03
7063	0.178	5.64	3.201	3.06	7.88	35.13	2.46
7064	0.155	5.50	2.107	3.12	7.38	30.19	2.08
7065	0.185	5.53	2.247	3.36	7.93	33.36	2.02
7066	0.175	5.46	2.792	3.27	7.03	36.12	1.90
7067	0.188	5.40	2.699	2.90	6.38	28.79	1.88
7068	0.233	6.15	3.102	3.32	7.67	35.65	2.80
7069	0.140	5.77	2.686	3.20	7.09	26.94	1.74
7070	0.198	6.25	2.826	3.37	8.21	35.35	2.31
Mean	0.1773	5.682	2.6712	3.214	7.387	31.893	2.139
SD	0.0264	0.294	0.3544	0.149	0.560	3.559	0.312
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Testes /TBW (Ratio)	Thymus /TBW (Ratio)
	-	-
7061	8.45	1.249
7062	7.92	0.966
7063	9.21	1.445
7064	8.86	1.058
7065	8.02	1.765
7066	7.61	1.391
7067	7.69	1.411
7068	9.86	1.945
7069	10.14	1.317
7070	8.80	1.391
Mean	8.657	1.3939
SD	0.885	0.2919
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Ovaries with oviducts/TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7011	0.314	9.43	3.76	8.20	34.07	0.639	2.01
7012	0.364	9.42	3.59	8.16	30.10	0.621	2.04
7013	0.316	8.05	3.76	7.78	29.44	0.571	2.26
7014	0.335	9.21	3.96	8.06	29.91	0.639	2.16
7015	0.292	8.81	3.81	6.99	31.02	0.589	1.78
7016	0.300	8.55	3.66	7.40	36.08	0.546	2.47
7017	0.327	9.46	3.46	7.32	29.51	0.507	2.29
7018	0.290	8.38	3.78	7.68	30.00	0.647	2.20
7019	0.329	8.54	3.54	7.75	32.25	0.450	2.75
7020	0.272	8.16	3.32	7.24	30.40	0.516	1.76
Mean	0.3139	8.801	3.665	7.657	31.278	0.5727	2.171
SD	0.0265	0.545	0.189	0.412	2.212	0.0669	0.300
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Thymus /TBW (Ratio)	Uterus /TBW (Ratio)
	-	-
7011	1.902	2.94
7012	1.252	2.91
7013	1.805	3.61
7014	2.026	2.86
7015	2.081	2.37
7016	2.119	2.11
7017	1.878	4.24
7018	1.548	4.02
7019	1.721	1.83
7020	2.532	4.68
Mean	1.8863	3.159
SD	0.3463	0.949
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Ovaries with oviducts/TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7031	0.308	8.63	3.76	8.03	33.63	0.504	2.61
7032	0.343	9.49	3.70	8.84	34.35	0.551	1.99
7033	0.392	9.26	3.64	8.99	34.75	0.650	2.49
7034	0.307	9.65	3.77	8.09	31.86	0.568	1.96
7035	0.292	8.24	3.65	6.91	32.75	0.609	1.85
7036	0.276	8.16	3.60	7.72	38.73	0.566	2.63
7037	0.324	10.33	4.12	8.63	32.58	0.527	2.14
7038	0.336	7.61	3.52	7.41	28.54	0.538	1.78
7039	0.288	8.89	3.58	8.23	35.47	0.510	2.51
7040	0.304	8.02	3.58	8.09	35.53	0.611	2.88
Mean	0.3168	8.828	3.692	8.094	33.819	0.5635	2.284
SD	0.0336	0.852	0.171	0.639	2.693	0.0474	0.384
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Thymus /TBW (Ratio)	Uterus /TBW (Ratio)
	-	-
7031	2.021	1.97
7032	2.065	2.50
7033	2.452	2.49
7034	2.472	2.06
7035	1.764	1.63
7036	2.105	1.89
7037	2.033	2.97
7038	2.530	1.82
7039	1.630	1.69
7040	1.669	1.60
Mean	2.0742	2.060
SD	0.3287	0.452
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Ovaries with oviducts/TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7051	0.258	9.86	3.78	7.88	32.49	0.618	2.53
7052	0.295	8.55	3.66	7.97	36.74	0.476	2.11
7053	0.247	8.38	3.44	6.56	30.53	0.470	2.15
7054	0.313	8.17	3.50	6.18	28.90	0.496	2.07
7055	0.253	7.90	3.58	7.70	30.54	0.545	1.87
7056	0.264	8.44	3.24	7.24	28.96	0.428	2.48
7057	0.230	8.87	3.69	7.88	32.93	0.604	2.52
7058	0.290	9.24	3.84	7.59	30.45	0.469	2.01
7059	0.310	7.90	3.59	7.82	26.49	0.581	2.10
7060	0.351	9.60	3.73	8.22	33.56	0.538	1.64
Mean	0.2812	8.692	3.605	7.505	31.158	0.5222	2.149
SD	0.0372	0.686	0.178	0.657	2.883	0.0643	0.291
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Thymus /TBW (Ratio)	Uterus /TBW (Ratio)
	-	-
7051	1.820	2.12
7052	2.559	1.89
7053	1.802	5.22
7054	1.378	2.20
7055	2.078	2.45
7056	2.540	1.80
7057	2.392	2.21
7058	1.621	1.92
7059	1.754	3.63
7060	2.240	2.36
Mean	2.0184	2.579
SD	0.4057	1.063
N	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Ovaries with oviducts/TBW (Ratio)	Spleen /TBW (Ratio)
	-	-	-	-	-	-	-
7071	0.277	8.64	3.45	7.53	34.81	0.613	2.55
7072	0.319	8.71	3.66	8.06	33.06	0.612	2.33
7073	0.299	7.95	3.73	7.05	31.80	0.574	2.09
7074	0.290	9.41	3.53	8.60	32.35	0.475	1.76
7075	0.342	9.11	3.60	8.00	39.29	0.644	2.13
7076	0.342	8.63	3.50	8.63	35.56	0.620	2.26
7077	0.251	8.04	3.49	7.33	30.39	0.494	2.12
7078	0.369	8.69	3.74	8.06	31.94	0.581	2.21
7079	0.371	8.23	3.99	6.85	29.80	0.645	2.34
7080	0.297	9.23	3.56	7.70	33.69	0.577	2.12
Mean	0.3157	8.664	3.625	7.783	33.269	0.5835	2.191
SD	0.0399	0.492	0.163	0.602	2.772	0.0581	0.206
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Thymus /TBW (Ratio)	Uterus /TBW (Ratio)
	-	-
7071	2.736	1.96
7072	1.978	2.24
7073	1.553	2.13
7074	1.715	2.35
7075	1.956	2.22
7076	2.842	2.09
7077	2.416	1.49
7078	2.631	1.85
7079	1.774	2.26
7080	2.761	2.43
Mean	2.2362	2.103
SD	0.4918	0.277
N	10	10

APPENDIX S: INDIVIDUAL ANIMAL ORGAN-TO-BRAIN WEIGHT RATIOS[1,2]

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] [organ weight/brain weight]

[2] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.

Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.

Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	Adrenal /BrW (Ratio)	Epididymides /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Testes /BrW (Ratio)
	-	-	-	-	-	-	-
7001	0.033	0.521	0.60	1.46	5.06	0.39	1.67
7002	0.033	0.435	0.52	1.30	6.51	0.36	1.01
7003	0.033	0.437	0.55	1.24	5.83	0.40	1.52
7004	0.028	0.414	0.54	1.14	5.56	0.36	1.23
7005	0.030	0.495	0.51	1.05	4.02	0.36	1.39
7006	0.030	0.545	0.59	1.15	5.41	0.45	1.42
7007	0.032	0.549	0.63	1.33	5.48	0.49	1.86
7008	0.032	0.471	0.53	1.17	4.27	0.41	1.51
7009	0.031	0.465	0.56	1.24	4.88	0.39	1.62
7010	0.023	0.480	0.55	1.25	5.37	0.28	1.48
Mean	0.0306	0.4813	0.558	1.232	5.238	0.388	1.469
SD	0.0031	0.0465	0.038	0.114	0.727	0.057	0.235
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

0 mg/kg/day Group 1	Thymus /BrW (Ratio)
	-
7001	0.386
7002	0.270
7003	0.230
7004	0.194
7005	0.301
7006	0.180
7007	0.309
7008	0.187
7009	0.237
7010	0.140
Mean	0.2436
SD	0.0739
N	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Adrenal /BrW (Ratio)	Epididymides /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Testes /BrW (Ratio)
	-	-	-	-	-	-	-
7021	0.039	0.597	0.58	1.37	5.64	0.41	1.73
7022	0.033	0.498	0.58	1.36	5.22	0.38	1.40
7023	0.024	0.536	0.58	1.11	4.86	0.35	1.33
7024	0.029	0.468	0.55	1.11	4.65	0.32	1.47
7025	0.033	0.502	0.54	1.16	5.14	0.41	1.51
7026	0.024	0.539	0.58	1.32	5.65	0.42	1.82
7027	0.040	0.470	0.60	1.23	4.92	0.32	1.59
7028	0.027	0.495	0.53	1.25	4.99	0.49	1.70
7029	0.028	0.416	0.70	1.36	5.67	0.33	1.61
7030	0.028	0.574	0.62	1.24	5.54	0.39	1.65
Mean	0.0307	0.5095	0.585	1.251	5.228	0.380	1.581
SD	0.0056	0.0535	0.048	0.100	0.374	0.055	0.155
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

512 mg/kg/day Group 2	Thymus /BrW (Ratio)
	-
7021	0.183
7022	0.282
7023	0.235
7024	0.277
7025	0.194
7026	0.299
7027	0.333
7028	0.287
7029	0.291
7030	0.250
Mean	0.2630
SD	0.0472
N	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date -

1024 mg/kg/day Group 3	Adrenal /BrW (Ratio)	Epididymides /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Testes /BrW (Ratio)
	-	-	-	-	-	-	-
7041	0.031	0.518	0.52	1.31	6.12	0.37	1.62
7042	0.032	0.467	0.60	1.27	5.77	0.34	1.31
7043	0.026	0.435	0.57	1.17	4.87	0.36	1.60
7044	0.029	0.579	0.58	1.27	5.91	0.32	1.61
7045	0.028	0.418	0.56	1.09	5.28	0.30	1.47
7046	0.026	0.423	0.64	1.37	5.83	0.36	1.39
7047	0.025	0.524	0.70	1.49	6.71	0.44	1.67
7048	0.029	0.459	0.57	1.34	6.52	0.34	1.38
7049	0.017	0.439	0.53	1.18	4.52	0.37	1.49
7050	0.027	0.476	0.55	1.28	4.80	0.33	1.44
Mean	0.0270	0.4738	0.583	1.278	5.633	0.353	1.498
SD	0.0043	0.0521	0.052	0.114	0.740	0.039	0.123
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Thymus /BrW (Ratio)
	-
7041	0.233
7042	0.233
7043	0.206
7044	0.215
7045	0.248
7046	0.370
7047	0.295
7048	0.265
7049	0.193
7050	0.242
Mean	0.2502
SD	0.0514
N	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Adrenal /BrW (Ratio)	Epididymides /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Testes /BrW (Ratio)
	-	-	-	-	-	-	-
7061	0.031	0.498	0.58	1.25	5.22	0.39	1.54
7062	0.027	0.411	0.59	1.32	5.09	0.36	1.40
7063	0.032	0.568	0.54	1.40	6.23	0.44	1.63
7064	0.028	0.383	0.57	1.34	5.49	0.38	1.61
7065	0.033	0.406	0.61	1.43	6.03	0.37	1.45
7066	0.032	0.512	0.60	1.29	6.62	0.35	1.40
7067	0.035	0.500	0.54	1.18	5.33	0.35	1.42
7068	0.038	0.505	0.54	1.25	5.80	0.45	1.60
7069	0.024	0.465	0.55	1.23	4.67	0.30	1.76
7070	0.032	0.452	0.54	1.31	5.66	0.37	1.41
Mean	0.0312	0.4700	0.566	1.300	5.614	0.376	1.523
SD	0.0039	0.0573	0.027	0.078	0.579	0.044	0.125
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Thymus /BrW (Ratio)
	-
7061	0.228
7062	0.171
7063	0.256
7064	0.193
7065	0.319
7066	0.255
7067	0.261
7068	0.316
7069	0.228
7070	0.223
Mean	0.2450
SD	0.0476
N	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Ovaries with oviducts/BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)
	-	-	-	-	-	-	-
7011	0.033	0.40	0.87	3.61	0.068	0.21	0.202
7012	0.039	0.38	0.87	3.20	0.066	0.22	0.133
7013	0.039	0.47	0.97	3.66	0.071	0.28	0.224
7014	0.036	0.43	0.88	3.25	0.069	0.23	0.220
7015	0.033	0.43	0.79	3.52	0.067	0.20	0.236
7016	0.035	0.43	0.87	4.22	0.064	0.29	0.248
7017	0.035	0.37	0.77	3.12	0.054	0.24	0.198
7018	0.035	0.45	0.92	3.58	0.077	0.26	0.185
7019	0.039	0.41	0.91	3.78	0.053	0.32	0.201
7020	0.033	0.41	0.89	3.73	0.063	0.22	0.310
Mean	0.0357	0.418	0.872	3.566	0.0652	0.248	0.2158
SD	0.0024	0.031	0.056	0.325	0.0075	0.039	0.0459
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Uterus /BrW (Ratio)
	-
7011	0.31
7012	0.31
7013	0.45
7014	0.31
7015	0.27
7016	0.25
7017	0.45
7018	0.48
7019	0.21
7020	0.57
Mean	0.361
SD	0.118
N	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Ovaries with oviducts/BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)
	-	-	-	-	-	-	-
7031	0.036	0.44	0.93	3.90	0.058	0.30	0.234
7032	0.036	0.39	0.93	3.62	0.058	0.21	0.218
7033	0.042	0.39	0.97	3.75	0.070	0.27	0.265
7034	0.032	0.39	0.84	3.30	0.059	0.20	0.256
7035	0.035	0.44	0.84	3.97	0.074	0.22	0.214
7036	0.034	0.44	0.95	4.75	0.069	0.32	0.258
7037	0.031	0.40	0.84	3.15	0.051	0.21	0.197
7038	0.044	0.46	0.97	3.75	0.071	0.23	0.332
7039	0.032	0.40	0.93	3.99	0.057	0.28	0.183
7040	0.038	0.45	1.01	4.43	0.076	0.36	0.208
Mean	0.0361	0.420	0.920	3.862	0.0644	0.261	0.2366
SD	0.0043	0.028	0.062	0.476	0.0086	0.054	0.0434
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

512 mg/kg/day Group 2	Uterus /BrW (Ratio)
	-
7031	0.23
7032	0.26
7033	0.27
7034	0.21
7035	0.20
7036	0.23
7037	0.29
7038	0.24
7039	0.19
7040	0.20
Mean	0.232
SD	0.033
N	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Ovaries with oviducts/BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)
	-	-	-	-	-	-	-
7051	0.026	0.38	0.80	3.29	0.063	0.26	0.185
7052	0.035	0.43	0.93	4.30	0.056	0.25	0.299
7053	0.029	0.41	0.78	3.64	0.056	0.26	0.215
7054	0.038	0.43	0.76	3.54	0.061	0.25	0.169
7055	0.032	0.45	0.98	3.87	0.069	0.24	0.263
7056	0.031	0.38	0.86	3.43	0.051	0.29	0.301
7057	0.026	0.42	0.89	3.71	0.068	0.28	0.270
7058	0.031	0.42	0.82	3.29	0.051	0.22	0.175
7059	0.039	0.45	0.99	3.35	0.073	0.27	0.222
7060	0.037	0.39	0.86	3.50	0.056	0.17	0.233
Mean	0.0325	0.416	0.866	3.592	0.0603	0.248	0.2332
SD	0.0047	0.026	0.080	0.310	0.0079	0.035	0.0489
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female   Day(s) Relative to Start Date

1024 mg/kg/day Group 3	Uterus /BrW (Ratio)
	-
7051	0.21
7052	0.22
7053	0.62
7054	0.27
7055	0.31
7056	0.21
7057	0.25
7058	0.21
7059	0.46
7060	0.25
Mean	0.301
SD	0.136
N	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Ovaries with oviducts/BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)
	-	-	-	-	-	-	-
7071	0.032	0.40	0.87	4.03	0.071	0.30	0.317
7072	0.037	0.42	0.93	3.80	0.070	0.27	0.227
7073	0.038	0.47	0.89	4.00	0.072	0.26	0.195
7074	0.031	0.38	0.91	3.44	0.050	0.19	0.182
7075	0.038	0.40	0.88	4.31	0.071	0.23	0.215
7076	0.040	0.41	1.00	4.12	0.072	0.26	0.329
7077	0.031	0.43	0.91	3.78	0.061	0.26	0.300
7078	0.042	0.43	0.93	3.67	0.067	0.25	0.303
7079	0.045	0.49	0.83	3.62	0.078	0.28	0.216
7080	0.032	0.39	0.83	3.65	0.062	0.23	0.299
Mean	0.0365	0.420	0.898	3.842	0.0676	0.254	0.2583
SD	0.0050	0.036	0.049	0.267	0.0078	0.031	0.0561
N	10	10	10	10	10	10	10

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

1536 mg/kg/day Group 4	Uterus /BrW (Ratio)
	-
7071	0.23
7072	0.26
7073	0.27
7074	0.25
7075	0.24
7076	0.24
7077	0.19
7078	0.21
7079	0.27
7080	0.26
Mean	0.242
SD	0.028
N	10