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
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1111 Pennsylvania Ave, NW
Washington, DC 20004
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8. Exemptions from FOIA Disclosure:

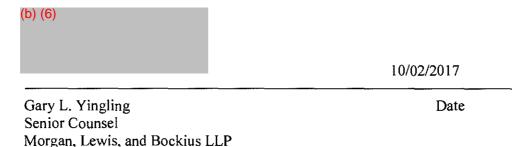
The information provided in this application does not contain confidential or proprietary information, and therefore no FOIA exemptions are claimed.

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:



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%

¹Miscellaneous 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.

			 		<u> </u>	
	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%
рН	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

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.

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.

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

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.

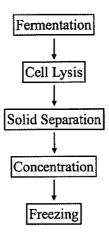
2.6.3 Recovery Process

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.

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, >10⁴ 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 (*pAOXI*). This promoter has been demonstrated to produce high levels of recombinant proteins after producing biomass on glycerol, and inducing *pAOXI* 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

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

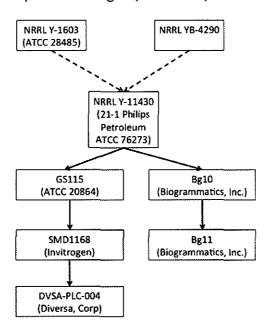
³ The NRRL collection is now known as the Agriculture Research Service Culture Collection and is at the Microbial Genomics and Bioprocessing Research Unit (MGB) of the National Center for Agricultural Utilization Research (NCAUR) in Peoria, IL.

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)

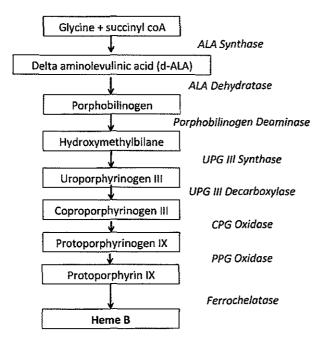


2.7.3 Construction of the Production Strain

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 hemebound 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 (Pmel) 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

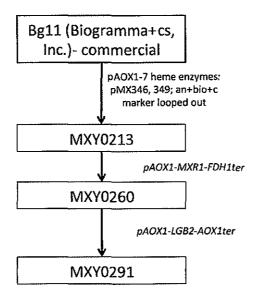
Mxr1 is a transcriptional activator of the pAOX1 promoter. The presence of Mxr1 leads to improved production of the recombinant protein leghemoglobin. A linear cassette of DNA

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 *pAOXI-LGB2-AOXIter* 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" 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 90^{th} 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 90^{th} 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.

⁶http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ingredientsadditivesgraspac kaging/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 (O₂) or the structurally similar carbon dioxide (CO₂), 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., 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 to 10% 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 ≥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

14-Day non-GLP Dietary Toxicity and Palatability Study in Rats (Study 43167)

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	Target Exposure of Soy Leghemoglobin (mg/kg/day)
1	10/10	(mg/kg/day)	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 <u>28-Day Investigative Study in Rats with 14-Day Estrous Cycle Pre-Screen</u> (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.

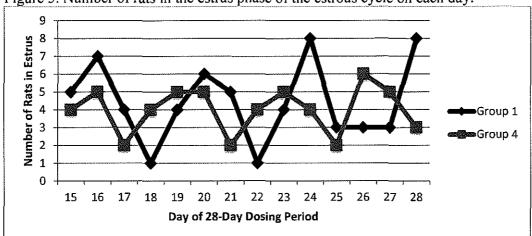


Figure 5. Number of rats in the estrus phase of the estrous cycle on each day.

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 ne	cropsy observations in the uterus.
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	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. <u>Pathology Peer Review on 28-Day GLP Dietary Toxicity Study in Rats</u> (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-

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:

 $[\]frac{https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Ingredients}{AdditivesGRASPackaging/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 <u>Bacterial Reverse Mutation Assay</u>

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 (chemicallyinduced 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 <u>In Vitro Mammalian Chromosome Aberration Test in Human Lymphocytes</u>

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 μ g/mL soy leghemoglobin; Experiment II: 100, 200, 500 and 1000 μ g/mL soy leghemoglobin. In Experiment II, precipitation occurred at concentrations 500 μ g/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 μ g/mL (69%), 2500 μ g/mL (56%) and 5000 μ g/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. 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 μ g/mL (69%), 1000 μ g/mL (53%), 2000 μ g/mL (26%), 3000 μ g/mL (13%), 4000 μ g/mL (38%) and 5000 μ g/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 μ g/mL. In experiment I, no biologically relevant decreases of the proliferation index were reported at concentrations up to 5000 μ g/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 μ g/mL groups were 1.23 and 1.12. Decrease of 79% at 500 μ g/mL and 72% at 1000 μ g/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 μ g/mL) and CPA (7.5 μ g/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. 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 peanutallergic 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

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	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	Blag3	37%	64%
		CAY69138.1	525	Cla h 10	72.50%	
Hypothetical protein PAS	238031215			Alt a 10	72.50%	69%
protein 1 A5				Lep d 13	35.40%	
Mitochondrial				Cla h 10	76.20%	
aldehyde dehydrogenase	238033249	CAY71271.1	501	Alt a 10	76.20%	62%
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				Mala f 4	70%	57%
dehydrogenase	238034064	CAY72086.1	342	Pis s 2	36.20%	
Putative protein, unknown function	238033788	CAY71810.1	328	n/a	n/a	86%
	238032989	CAY71012.1	248	Tri a 31	62.50%	
Triose phosphate				Der f 25.0101 (isoform)	60.00%	71%
isomerase				Der f 25.0201 (isoform)	60.00%	7170
				Crac8	57.50%	
				Mala s 6	87.50%	
				Asp f 27	85%	
				Cat r I	81.30%	
Hypothetical				Der f 29	80%	
protein	328350030	CCA36430.1	161	Asp f 11	80%	74%
(cyclophilin) PP7435				Bet v 7	80%	
11/433				(Unassigned by IUIS) PPIase ⁶ from Dauces carota	78%	
Cytosolic				Ole e 5		
superoxide dismutase	238034030	CAY72052.1	154	23 isoforms	60% - 55%	79%

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

¹AA: amino acids;

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. 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

²AOL: AllergenOnline

³Allergen name in IUIS allergen list unless denoted as unassigned by IUIS;

⁴ID: identity (%);

⁵n/a: not available or no answer. ⁶PPIase: 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 partoria proteins of interest, these proteins were uniquitous and highly conserved

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/predi ct.html	Weighted average assessment based on SVM and sequence searches suggested by FAO*	Non allergen	
AlgPred	http://webs.iiitd.edu.in /raghava/algpred/subm ission.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.c gi	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/aller genIntroduction.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 peerreviewed 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 ug 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.

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/Ingredients AdditivesGRASPackaging/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

04 August 2017

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.

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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

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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%
рH	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 estimates¹. 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 Consumptio n (g/day) ²	Anticipated Market Share Replaceme nt (%)	Anticipate d Typical Use rate (%)	Soy Leghemoglobi n Estimated Typical Daily Intake (mg/person/da y)	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 Consumptio n (g/day)	Anticipated Market Share Replaceme nt (%)	Anticipate d Typical Use rate (%)	LegH Prep Dry Solids Estimated Typical Daily Intake (mg/person/da y)	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*.

http://www.ncaur.usda.gov/SP2UserFiles/Place/12355000/pdf/ficrcd/FICRCD Intake Tables 2007 08.pdf

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.

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

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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 Preprelated 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

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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

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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.

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		09 August 2017
Professor/Joseph F. B	orźelleca, Ph.D.	Date
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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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- Annex 10. Leghemoglobin Preparation in vitro digestibility study in human simulated gastric fluid

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 \sim 415 nm. At pH 2, the heme co-factor has dissociated from the denatured polypeptide, as indicated by the broad Soret peak at \sim 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.

References:

M. Punta, P.C. Coggill, R.Y. Eberhardt, J. Mistry, J. Tate, C. Boursnell, N. Pang, K. Forslund, G. Ceric, J. Clements, A. Heger, L. Holm, E.L.L. Sonnhammer, S.R. Eddy, A. Bateman, R.D. Finn. (2012). Nucleic Acids Research Database Issue 40:D290--- D301

Delano WL (2007) The PyMOL Molecular Graphics System (DeLano Scientific, San Carlos, CA).

Konermann, L., Rosell, F. I., Mauk, a. G., Douglas, D. J. (1997). Acid-induced denaturation of myoglobin studied by time-resolved electrospray ionization mass spectrometry. Biochemistry. 36: 6448-6454.

Sepe, H. A., Faustman, C., Lee, S., Tang, J., Suman, S. P., & Venkitanarayanan, K. S. (2005). Effects of reducing agents on premature browning in ground beef. Food Chemistry, 93, 571–576

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).

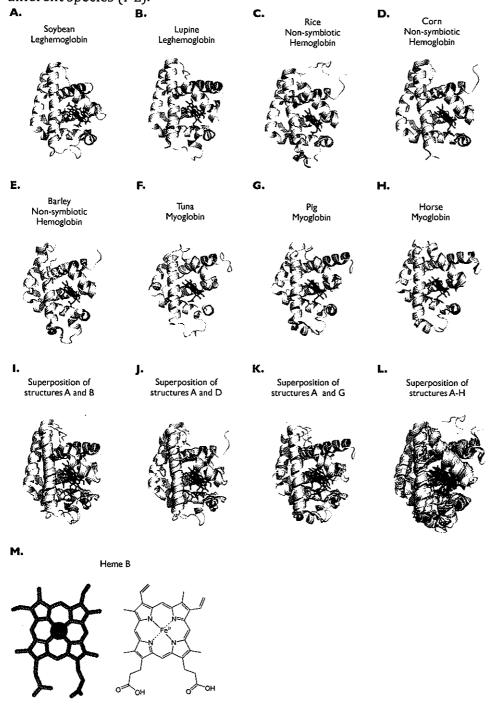
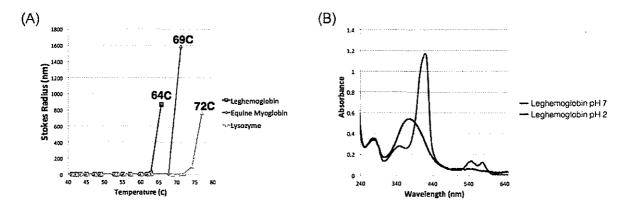


Table 1. Structural comparison between plant hemoglobins and animal myoglobins. Root-mean-square-deviation (RMSD) between all backbone atoms of superimposed X-ray crystallography protein structures (respective PDB codes are shown in parenthesis).

Species			
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 (20IF)	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

Page 1 of 593

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)	1 ,
Study Director:	Date: 7 96 17
Name of Signer: Mithila Shitut, BVSc & AH, MS	
Name of Company: Product Safety Labs	
(b) (6)	
Sponsor:	Date: 7/26/17
Name of Signer: Rachel Fraser, PhD	, ,
Name of Company: Impossible Foods Inc.	
(b) (6)	
Submitter	Date: 7/26/17
Name of Signer: Rachel Frascr, 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)

Maryann Zakrzewski X Quality Assurance Auditor Product Safety Labs JU/4 +4, +017

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)	
	36 July 2017
Mithila Shitut, BVSc & AH, MS Study Director	Date
Product Safety Labs	
(b) (6)	
	26 - July 2017
Odete Mendes, DVM, PhD, DACVP, DABT	Date

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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

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Principal Investigator: Rachel Fraser, PhD

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Daniel G. Branstetter, DVM, PhD, DACVP

Histopathology Peer Review

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P.I. (pathology): Karen Regan, DVM, DABT, DACVP

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 respectively. 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 parameters 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 $\pm 20\%$ 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 $\pm 20\%$ 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 \pm 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 μ L 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 μ L 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)pHketone (KET)color (COL)glucose (UGLC)bilirubin (UBIL)clarity (CLAR)specific gravity (SG)blood (BLD)volume (UVOL)protein (UMTP)urobilinogen (URO)

microscopic urine sediment examination

and lumbar

Product Safety Labs

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

brain - 3 sections including

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

accessory genital organs ileum with Peyer's patches rectum
(prostate and seminal vesicles) jejunum salivary glands (sublingual adrenals kidneys submandibular, and all gross lesions larynx parotid)
aorta liver skeletal muscle

bone (femur) lungs skin

bone marrow (from femur & lymph node mandibular spinal cord – 3 levels: sternum) lymph node mesenteric cervical, mid-thoracic,

medulla/pons, cerebellar, nasal turbinates spleen and cerebral cortex nose sternum cecum ovaries stomach cervix oviducts thymus colon pancreas thyroid duodenum parathyroid trachea esophagus peripheral nerve (sciatic) urinary bladder

mammary gland

Harderian gland pharynx uterus heart pituitary gland vagina

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 (ProvantisTM 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.	

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

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 respectively. 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 parameters 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 parameters 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%

Final Sample – Initial Sample x 100
Initial Sample

TABLE 1B: CHEMICAL ANALYSIS RESULTS

Results for Dietary Stability of Initial Samples

Day	Group	Target Concentration Test Substance (ppm)	Measured Concentration Test Substance (ppm)	% of Target ²
	1 (BO)	0	ND	NA
	2 (M)	4373	4508	103.08%
	2 (F)	4711	4645	98.61%
0	3 (M)	8746	7951	90.91%
	3 (F)	9422	9034	95.89%
	4(M)	13118	12265	93.50%
	4(F)	14133	12808	90.62%
	1 (BO)	0	ND	NA
	2 (M)	4373	4207	96.20%
	2 (F)	4711	4471	94.90%
4	3 (M)	8746	8238	94.19%
	3 (F)	9422	8918	94.65%
	4(M)	13118	12097	92.22%
	4(F)	14133	13191	93.33%
	1 (BO)	0	ND	NA
	2 (M)	4373	4202	96.09%
	2 (F)	4711	4468	94.84%
7	3 (M)	8746	8200	93.76%
	3 (F)	9422	8728	92.63%
	4(M)	13118	12423	94.70%
	4(F)	14133	13547	95.85%
	1 (BO)	0	ND	NA
	2 (M)	4373	3968	90.74%
	2 (F)	4711	4693	99.63%
10	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 (%)
	1 (BO)	Middle	0	ND	NA	NA	NA
		Тор		4302	98.38%		
	2 (M)	Middle	4373	4061	92.86%	95.87%	2.92%
		Bottom		4215	96.38%		
		Тор		4853	103.01%		
	2 (F)	Middle	4711	4583	97.28%	98.01%	4.77%
		Bottom		4416	93.74%		
	3 (M)	Тор	8746	8636	98.74%	95.40%	3.09%
		Middle		8145	93.13%		
0		Bottom		8250	94.33%		
	3 (F)	Тор	9422	9669	102.62%	97.71%	5.50%
		Middle		9284	98.53%		
		Bottom		8666	91.98%		
	4 (M)	Тор		12226	93.20%		5.24%
		Middle	13118	13558	103.35%	97.85%	
		Bottom		12724	97.00%		
		Тор		14567	103.07%		
	4 (F)	Middle	14133	14183	100.35%	98.64%	5.57%
		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
	1 (BO)	0	ND	NA
0^3	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 OBSERVATIONS¹

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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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

.....

						PSL Study Number 43166
	Day	numbers relativ	e to Start Date		•••••	
Sex: Female		O mg/kg/day	512 mg/kg/day	1024 mg/kg/day	1536 mg/kg/day	
	Alopecia Number of Observations		10			
	Number of Animals Days from - to	•	1 21 30	•	•	

TABLE 3: SUMMARY OF DETAILED CLINICAL OBSERVATIONS¹

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

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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 WEIGHTS¹

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)	dyweight (g)	
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Sex: Male		0 mg/kg/day Group 1	512 mg/kg/dny Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to	Start Date				
0	Mean	236.4 11	236.4	236.7	236.3
	SD	6.1	6.1	7.0	6.7
	N	10	10	10	10
7	Mean	287.7 11	289.6	290.9	292.8
	SD	14.0	11.1	14.3	12.2
	N N	10	01	10	10
14	Mean	יו 332.3	337.0	341.6	339.5
	SD	16.5	18.4	24.2	18.6
	N	10	10	10	10
21	Mean	יו 373.2	376.6	384.5	379.9
	SD	22.7	21.4	31.1	22.7
	N	10	10	10	10
28	Mean	394.7 11	398.9	410.2	405.5
	SD	28.8	26.4	37.2	24.4
	N	10	10	10	10

^{1 [1 -} Automatic Transformation: Identity (No Transformation)]

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Sex: 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
Day(s) Relative to S	Start Date				
0	Mean	174.1 11	174.4	175.6	174.3
	SD	12.3	12.6	11.8	11.9
	N	10	10	10	10
7	Mean	198.3 11	201.0	204.0	199.3
	SD	14.8	16.5	13.3	10.5
	N	10	10	10	10
14	Mean	218.8 11	218.5	223.7	221.3
	SD	21.9	19.6	14.6	14.3
	N	10	10	10	10
21	Mean	239.2 11	229.1	238.8	238.0
	SD	24.0	19.4	19.4	13.1
	N	10	10	10	10
28	Mean	249.8 11	244.0	253.2	248.7
	SD	24.0	23.3	17.7	12.4
	N	10	10	10	10

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

TABLE 5: SUMMARY OF MEAN DAILY BODY WEIGHT GAIN¹

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	n
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Sex: Male		0 mg/kg/day Group I	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to S	tart Date				
0 → 7	Mean	7.33 11	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 11	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 11	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 11	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 11	5.80	6.20	6,04
	SD	0.84	0.83	1.14	0.70
	N	10	10	10	10
	1			1	

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

Mean Daily Body Weight Gain (g/day)

Sex: 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
Day(s) Relative to St	art Date				
0 7	Mean	3.46 11	3.80	4.06	3.57
	SD	1.03	0.96	0.72	0.61
	N	ιo	10	10	10
7 14	Mean	2.93 R*	2.50	2.81	3.14
	SD	2.09	0.75	0.66	0.81
	N	10	10	10	10
14> 21	Mean	2.911,A3	1.51 DD	2.16	2.39
	SD	1.15	0.82	1.03	0.96
	N N	10	10	10	10
21 → 28	Mean	1.51 L4	2.13	2.06	1.53
	GZ	1.03	0.85	0.63	0.79
	N N	10	10	10	10
0 → 28	Mean	2.70 1	2.49	2.77	2.66
	SD	0.60	0.53	0.30	0.34
	N N	10	10	10	10

^{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 CONSUMPTION1

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.

14	Daile	Cand.	Consumption	- Caldani
Mean	Daily	roon	Consumunt	m rozanyi

Sex: Male		O mg/kg/dny Group I	512 mg/kg/đay Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to St	lart Date				
0 3	Mean	18.73 R1	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 [†]	28.60	28.23	28.63
	SD	1.08	0.52	2.08	1.07
	N N	10	10	10	10
0 -+ 7	Mean	24.04 R3	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 Ri	27.10	27.80 dd²	27,90 d ³
	SD	1.31	0.81	1.97	0.78
	N	10	10	10	10
10> 14	Mean	26.55 R1	27.25	27.88	27.45
	SD	1.17	0.91	2.25	1.03
	N N	10	10	10	10
7 14	Mean	26,44 R1	27.19	27.84 d ³	27.64
	SD	1.16	0.84	2.12	0.84
	א	10	10	10	10
14 17	Mean	25.90 R1	25.47	26.33	26.17
	SD	0.89	1.83	2.71	0.82
	N L	10	10	10	10
17 → 21	Mean	26.38 R1	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 R1	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'	23.07	22.27	22.47
	SĐ	0.77	1.03	1.61	0.66
	N	10	10	10	10
24 28	Menn	27.70 R1	28.75	29.13	29.18
	SD	1.04	1.21	1.92	1.28
	N	10	10	10	10

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

Mean Daily Fo	od Consumption	(g/day)
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Sex: Male		0 mg/kg/day Group l	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to St	art Date				
21 → 28	Mean	25.17 R1	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 R1	25.88	26.25	26.26
	SD	0.91	0.87	1.58	0,90
	N	10	10	10	10

¹ JR - Automatic Transformation: Rank)

Mean Daily Food Consumption (g/day)

ex: Female		0	512	1024	1536
A. Pemare		mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
		Стоцр]	Group 2	Group 3	Group 4
ay(s) Relative to St	tart Date				
0 → 3	Mean	13.43 R*	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 R1	21.23	21.05	20.18
	SD	1.24	1.13	1.31	0.77
	N N	10	10	10	10
0 7	Mean	17.86 R ^s	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 ³	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 12	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 R1	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 12	19.40	18.47	18.73
	SD	1.34	0.76	1.22	1.17
	N	10	10	10	10
ŧ7 → 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 R1	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 12	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 R1	21.33	21.08	20.45
	SD	1.38	1.44	0.91	0.55
	l N.	10	10	10	10

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

Mean Daily	Food	Consumption	(g/day)

Sex: Female		0 mg/kg/day Group I	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to St	art Date	B-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1			
21 → 28	Mean	18.64 R1	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 17	19.05	18.79	[8,44
	SD	1.23	0.81	1.09	0.61
	l N	10	10	10	10

^{1 [}R - Automatic Transformation: Rank] 2 § - Automatic Transformation: Identity (No Transformation)]

TABLE 7: SUMMARY OF FOOD EFFICIENCY^{1,2}

¹ Food efficiency = <u>Mean Daily Body Weight Gain</u> 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		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to S	art Date				
0 → 7	Mean	0.304 11	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 [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 L²	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 11	0.123	0.139	0.139
	SD	0.040	0.032	0.040	910.0
	N	10	10	10	10
0 → 28	Mean	0.222 11	0.224	0.235	0.230
	SD	0.031	0.028	0.034	0.027
	N	10	10	10	10

^{1 [] -} Automatic Transformation: Identity (No Transformation)]
2 [L - Automatic Transformation: Log]

Food	1200	::	
rood	EH	ıcıc	ncv

Sex: 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
Day(s) Relative to S	tart Date				
0+ 7	Mean	0.193 11	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	0.1491,A1	0.077 DD	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 11	0.131	0.147	0.144
	SD	0.027	0.028	110.0	0.019
	N	10	10	10	10

^{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 PREPARATION¹

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		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
Day(s) Relative to St	art Date				
0 7	Mean	0,0	485.4	966.5	1459.8
	SD	0.0	20.9	42.5	103.0
	N	10	10	10	ιo
7 14	Mean	0.0	540.5	1095.9	1631.5
	SD	0.0	24.5	53.5	78.9
	N N	10	10	10	10
L4 ···• 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 N	10	10	10	10

Sex: 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
Day(s) Relative to S	tart Date				
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	ιo	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
	\$D	0.0	42.8	29.0	88.2
	N	10	10	10	10

TABLE 9: SUMMARY OF HEMATOLOGY VALUES¹

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

Sex Male			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to	Start Date	·		'	
RBC	22	Mean	7.72	7.60	7.61	7.70
(x10^6/µL)		SD	0.23	0.34	0.35	0.27
		N	10	10	10	10
		%Diff		-1.6	-1.5	-0.3
HGB	22	Mean	15.6	15.4	15.5	15.9
(g/dL)		SD	0.3	0.6	0.6	0.4
		N N	10	10	10	10
		%Diff		-1.5	-1.0	1.4
HCT	22	Меал	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	22	Mean	58.9	59.3	59.3	59.7
(fL)		SD	1.0	2.3	1.5	1.9
		N	10	10	10	10
		%Diff		0.7	0.7	1.3
мсн	22	Mean	20.3	20.3	20.4	20.6
(pg)		SD	0.5	0.9	0.5	0.7
		N	10	10	10	10
		%Diff		0.2	0.6	1.6
MCHC	22	Mean	34.4	34.2	34.4	34.5
(g/dL)		SD	0.4	0.4	0.3	0.5
		N	10	10	10	10
		%Diff	<u> </u>	-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	22	Mean	1160	1202	1171	1227
(x10^3/µL)		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: Mate	D() D. 1.1		0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to	Start Date				
WBC	22	Mean	13.00	14.41	11.13	13.45
(x10^3/µL)		SD	1.33	2.67	1.82	4.41
		N	10	10	10	10
		%Diff		10.8	-14.4	3.4
ANEU	22	Mean	1.91	1.99	1.75	1.57
(x10^3/µL)		SD	0.67	0.43	0.43	0.62
		N	10	10	10	10
		%Diff		4.1	-8.1	-17.8
ALYM	22	Mean	10.49	11.79	8.86	11.29
(x10^3/µL)		SD	1.17	2.48	1.70	4.15
		N	10	10	10	10
		%Diff		12.4	-15.5	7.7
AMON	22	Mean	0.31	0.34	0.28	0.30
(x10^3/µL)		SD	0.10	0.11	0.05	0.10
		N	10	10	10	10
		%Diff		10.2	-9.8	-1.5
AEOS	22	Mean	0.12	0.13	0.11	0.11
(x10^3/µL)		SD	0,04	0.08	0.04	0.05
		N	10	10	10	10
		%Diff		4.4	-7.2	-7.6
ABAS	22	Mean	0.09	0.09	0.07	0.10
(x10 ⁴ 3/µL)		SD	0.03	0.04	0.02	0.08
		N	10	10	10	10
		%Diff		-5.0	-27.0	6.2
ALUC	22	Mean	0.08	0.08	0.06	0.08
(x10^3/µL)		SD	0.03	0.03	0.02	0.04
		N	10	10	10	10
		%Diff		-8.1	-27.0	-2.4
ARET	22	Mean	232.6	235.8	246.3	243.8
(x10^3/µL)		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]

ex: Female			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to	Start Date		0,0ap 2	5.00mp 0	J.72p .
RBC	22	Mean	7.59	8.01 #1	7.86	7.63
(x10^6/µL)		SD	0.24	0.38	0.24	0.30
		N	10	10	10	10
		%Diff		5.6	3.6	0.6
HGB	22	Mean	15.3	16.2 #1	15.7	15.5
(g/dL)		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	22	Mean	57.5	57.4	56.8	57.7
(fL)		SD	1.1	2.2	1.2	2.2
		N	10	10	10	10
		%Diff		-0.2	-1.1	0.4
MCH	22	Mean	20.2	20.2	20.0	20.3
(pg)		SD	0.3	0.7	0.5	0.7
		N	10	10	10	10
		%Diff		0.1	-1.0	0.3
MCHC	22	Mean	35.2	35.3	35.2	35.2
(g/dL)		SD	0.7	0.3	0.4	0.5
		N	10	10	10	10
		%Diff		0.3	0.1	0.0
RDW	22	Меап	11.3	11.3	11.2	11.5
(%)		SD	0.4	0.5	0.3	0.5
ł		N	10	10	10	10
		%Diff		0.1	-0.4	1.7
PLT	22	Mean	1190	1176	1230	1229
(x10^3/µL)		SD	108	127	115	114
1		N	10	10	10	10
l		%Diff	,	-1.1	3.4	3.3

ex: Female			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to St	tart Date	Citaly 1	Cloup I	0,00p.0	Oloup .
WBC	22	Mean	10.08	11.87	11.59	10.19
(x10^3/µL)		SD	1.70	1.75	3.35	3.72
į		N	10	10	10	10
		%Diff		17.7	15.0	1.1
ANEU	22	Mean	1,48	1,56	1.68	1,54
(x10^3/µL)		SD	0.30	0.58	0.85	1.10
		N	10	10	10	10
		%Diff		5.3	13.9	4.0
ALYM	22	Mean	8.15	9.74	9.29	8.21
(x10^3/µL)		SD	1.58	1.43	2.71	2.88
		N	10	10	10	10
		%Diff		19.5	14.0	0.7
AMON	22	Mean	0.25	0.29	0.33	0.22
(x10^3/µL)		SD	0.15	0.06	0.15	0.14
		N	10	10	10	10
		%Diff		16.7	32.5	-11.1
AEOS	22	Mean	0.11	0.13	0.15	0.12
(x10^3/µL)		SD	0.03	0.04	0,05	0.06
		N	10	10	10	10
		%Diff	-	21.4	35.8	9.0
ABAS	22	Mean	0.04	0,07 #1	0.06	0.05
(x10^3/µL)		SD	0.01	0.03	0.03	0.04
		N	10	10	10	10
	•	%Diff		93.2	64.1	46.7
ALUC	22	Mean	0,05	0.07	0.07	0.05
(x10^3/µL)		SD	0.02	0.02	0.03	0.04
		N	10	10	10	10
		%Diff		29.1	26.2	2.9
ARET	22	Меап	205,8	182.4	169.1 #1	184.2
(x10^3/µL)		SD	33.9	32.9	30.9	33.7
		N.	10	10	10	10
		%Diff	_	-11,3	-17.8	-10.5

TABLE 10: SUMMARY OF COAGULATION VALUES¹

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

Sex: Male Day(s) Relative to Start Date		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 SD N	10.7 0.3 10	10.7 0.4 10	10.6 0.2 10	10.6 0.2 10
APTT (sec)	29	Mean SD N	20.2 2.4 10	23.8 5.3 10	24.9 @¹ 6.9 10	23.9 @¹ 4.8 10

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 SD	10.0 0.2	9.8 0.2	10.0 0.3	9.8 0.2
		N	10	10	10	10
APTT	30	Mean	21.9	20.0	20,8	19.4
(sec)		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 VALUES¹

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

ex: Male			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
Day(s) Relative to Start Date			Group 1	Cloup 2	3,000	Cloup 4
AST	22	Mean	73	76	79	78
(U/L)		SD	8	9	7	8
		N N	5	9	6	8
		%Diff		4.0	7.5	6.9
ALT	22	Mean	29	28	28	30
(U/L)		SD	4	4	3	4
		N N	10	10	10	10
		%Diff		-3.1	-2.4	2.4
SDH	22	Mean	8.2	8.1	8.4	8.0
(U/L)		SD	1.4	1.7	2.4	1.4
		N	5	9	6	8
		%Diff		-0.8	2.7	-1.9
ALKP	22	Mean	183	216	216	205
(U/L)		SD	24	29	44	42
		N.	10	10	10	10
		%Diff		18.6	18.5	12.3
BiLI	22	Mean	0.17	0.17	0.18	0.18
(mg/dL)		SD	0.02	0.02	0.02	0.02
		N N	10	10	10	10
		%Diff		1.2	4.1	5.9
BUN	22	Mean	10	11	10	11
(mg/dL)		SD	1	1	1	2
		N	10	10	10	10
		%Diff		4.8	-3.В	1.0
CREA	22	Mean	0.22	0.23	0.23	0.21
(mg/dL)		SD	0.01	0.02	0.02	0.02
		N	10	10	10	10
		%Diff		3.6	4.1	-5.9
CHOL	22	Mean	76	73	72	67
(mg/dL)		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			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to Sta	art Date			·	
TRIG	22	Mean	66	67	67	68
(mg/dL)		SD	17	13	17	26
		N	10	10	10	10
		%Diff		1.8	0.9	2.4
GLUC	22	Mean	95	100	102	98
(mg/dL)		SD	12	9	13	8
		N	10	10	10	10
		%Diff		5.4	7.1	2.6
TP	22	Mean	6.0	6.1	6.2	6.0
(g/dL)		SD	0.2	0.2	0.2	0.2
		N	10	10	10	10
		%Diff	-	0.7	2.8	0.2
ALB	22	Mean	3.1	3.2	3.3 #1	3.2
(g/dL)		SD	0.1	0.1	0.1	0.1
		N	10	10	10	10
		%Diff		2.2	4.1	1.9
GLOB	22	Mean	2.9	2.8	2.9	2.8
(g/dL)		SD	0.1	0.2	0.1	0.2
ſ		N	10	10	10	10
		%Diff		-1.0	1.4	-1.7
CALC	22	Mean	10.4	10.4	10.4	10.5
(mg/dL)		SD	0.2	0.2	0.2	0.2
		N	10	10	10	10
		%Diff		-0.1	0.1	0.8
IPHS	22	Mean	8.6	8.7	8.8	8.6
(mg/dL)		SD	0.4	0.4	0.9	0.4
-		N.	5	9	6	8
		%Diff	-	0.6	2.1	-0.3
NA NA	22	Mean	140.5	142.1	141.1	141.7
(mmol/L)		SD	4.2	0.6	0.7	0.8
		N	10	10	10	10
		%Diff		1.1	0.4	0.9

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 (mmoVL)	22	Mean SD N %Diff	5.03 0.25 10	5.19 0.26 10 3.1	5.55 #' 0.61 10 10.4	5.10 0.25 10 1.4
CL (mmol/L)	22	Mean SD N %Diff	100.8 2.4 10	102.0 1.0 10 1.2	101.6 0.8 10 0.8	101.7 1.2 10 0.9

Sex: Female			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to S	tart Date		J. J	5.05p 0	, , , , , , , , , , , , , , , , , , ,
AST	22	Mean	69	69	64	65
(U/L)		SD	6	10	8	6
		N	9	9	10	10
		%Diff		-0.3	-7.4	-6.5
ALT	22	Mean	25	26	25	27
(U/L)		SD	4	5	6	5
		N	10	10	10	10
		%Diff		2.8	-0.4	5.2
SDH	22	Mean	8.7	8.1	8.0	9.9
(U/L)		SD	2.2	1.2	0.9	2.5
		N	9	9 .	10	10
		%Diff		-7,4	-9.0	12.9
ALKP	22	Mean	137	107 #¹	121	108 #1
(U/L)		SD	16	19	29	25
		N	10	10	10	10
		%Diff		-22.4	-12.1	-21.3
BìLi	22	Mean	0.18	0.19	0.20	0.19
(mg/dL)		SD	0.02	0.02	0.02	0.03
		N	10	10	10	10
		%Diff	<u></u>	8.4	10.6	7.8
BUN	22	Меал	12	11	12	12
(mg/dL)		SD	2	1	2	1
1		N	10	10	10	10
		%Diff		-11.5	-0.8	0.0
CREA	22	Mean	0.28	0.26	0.27	0.28
(mg/dL)		SD	0.02	0.02	0.03	0.03
1		N	10	10	10	10
		%Diff		-6.9	-2.9	1.1
CHOŁ	22	Mean	85	95	98	94
(mg/dL)		SD	11	19	19	22
		N	10	10	10	10
		%Diff	•	12.2	15.6	11.2

ex: Female			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to S	Start Date	Sidap .	J. J	0.044	STORP T
TRIG	22	Mean	37	38	46	35
(mg/dL)		SD	6	9	15	8
		N	10	10	10	10
		%Diff	i	3.5	24.9	-4.3
GLUC	22	Mean	118	103 #1	104 #1	110
(mg/dL)		SD	15	10	10	14
		N	10	10	10	10
		%Diff		-13.3	-12.0	-6.7
TP	22	Mean	6.4	6.7	6.8	6.7
(g/dL)		SD	0.3	0.4	0.3	0.4
		l N	10	10	10	10
		%Diff		5.1	5.6	3.7
ALB	22	Mean	3.5	3.7	3.7	3.6
(g/dL)		SD	0.2	0.2	0.2	0.3
		l N	10	10	10	10
		%Diff		4.0	4.6	3.4
GLOB	22	Mean	2.9	3.1	3.1 #1	3.0
(g/dL)		\$D	0.1	0.2	0.2	0.1
		N	10	10	10	10
		%Diff		6.6	6.9	4.1
CALC	22	Mean	10.5	10.9 #1	11.0 #1	10.7
(mg/dL)		SD	0.3	0.3	0.3	0.4
		N	10	10	10	10
		%Diff		3.8	5.1	1,8
IPHS	22	Mean	7.1	7.8	7.6	7.1
(mg/dL)		SD	0.5	0.6	0.4	0.8
		N	9	9	10	10
		%Diff		9.7	6.5	-0.6
NA	22	Mean	140.3	140.6	140.3	140.2
(mmoVL)		SD	1.1	0.6	0.7	1.1
		l N	10	10	10	10
		%Diff		0.2	0.0	0.0

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 SD N %Diff	4.56 0.33 10	4.63 0.38 10 1.5	4.72 0.21 10 3.5	4.74 0.38 10 4.0
CL (mmoVL)	22 .	Mean SD N %Diff	102.6 1.2 10	101.3 #1 1.4 10 -1.3	101.1 #' 1.0 10 -1.5	102.1 1.1 10 -0.5

TABLE 12: SUMMARY OF URINALYSIS VALUES¹

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

Sex: Male			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to Sta	art Date	·		,	
UVOL	22	Mean	11.7	11.5	12.3	14.3
(mL)		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	22	Mean	0.3	0.2	0.3	0.2
(EU/dL)		SD	0.3	0.0	0.3	0.0
		N	10	9	10	10
		%Diff		-28.6	0.0	-28.6
UMTP	22	Mean	104	241	124	111
(mg/dL)		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			0 mg/kg/day Group 1	250 mg/kg/day Group 2	500 mg/kg/day Group 3	750 mg/kg/day Group 4
	Day(s) Relative to Sta	art Date	·			
UVOL	22	Mean	7.8	6.8	6.5	6.6
(mL)		SD	6.4	5.1	3.0	4.1
·		N	10	10	10	10
		%Diff		-12.3	-15.9	-14.9
рН	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	22	Меал	0.2	0.2	0.2	0.3
(EU/dL)		SD	0.0	0.0	0.0	0.3
		N	10	10	10	10
		%Diff	,	0.0	0.0	40.0
UMTP	22	Mean	43	41	34	44
(mg/dL)		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 OBSERVATIONS¹

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 Rescort ALL	Male				Female			
	0 mg/lg/day Group 1	512 ng/kg/day Group 2	16/24 mg/kg/day Group 3	1535 mg/kg/day Group 4	ngAtgyday Group 1	512 mg/kg/day Group 2	t024 mg/tg/day Group 3	1535 mg/kg/day Group 4
Number of Animala	10	10	10	10	10	10	10	10
Number of Completed Animals	10	10	10	10	10	-01	10	10
spleen Substitled	10	10	10	10	10	10	t0	10
dioxe							1	
testss-combined Submitted	10	10	10	10				
right small; soft	1							
storus Submitted					10	10	10	10
fluid filled					4		1	
epididymides-combined								
Submitted	10	10	10	10				
nght smaß	1							

TABLE 14: SUMMARY OF MEAN TERMINAL BODY AND ORGAN WEIGHTS¹

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			0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
	Day(s) Relative to Sta	nt Date			4.00F	J. W. F.
Terminal	-	Mean	367.5	3725	384.0	379.3
BW (5)		SD	25.3	23.8	33.4	21.4
(g)		N	10	10	10	10
Adrenal	-	Mean	יו 0.0654	0,0655	0.0593	0.0672
Glands Wt (g)		SĐ	0.0068	0.0112	0.0116	0.0098
(9)		N	10	10	10	10
Brein	•	Mean	יו 2.141	2.143	2.186	2.152
W((g)		SD	0.095	0.110	0.140	0.105
(9)		N	10	10	10	10
Epididymides	-	Mean	1.032 🚶	1.088	1.035	1.008
Wt (g)		SD	0.123	0.083	0.131	0.100
(9)		N	10	10	10	10
Heart	-	Mean	1.195 1	1.254	1.272	1,219
Wt (g)	ļ	SD	0.104	0.121	0.113	0.088
(9)		N	10	10	10	10
Kidneys		Mean	2641 1	2.678	2.789	2.800
Wt (9)		SĐ	0.297	0.219	0.246	0.241
197		N	10	10	10	10
Liver	•	Mean	יו 11.218	11.182	12,317	12.093
W1 (g)		SD	1.657	0,691	1.804	1.452
		N	10	10	10	10
Spieen	-	Mean	יו 0.831	0.813	0.769	0.809
Wt (g)		SD	0.125	0.107	0.053	0.105
	:	N	10	10	10	10
Testes		Mean	3.148 R*	3.381	3.266	3.272
(g) W(SD	0.531	0.292	0.251	0.245
		N	10	10	10	10
Thymus	-	Mean	0.5205 11	0.5661	0.5466	0.5276
Wt (9)	i	SD	0.1595	0.1162	0.1185	0,1097
(9)		N	10	10	10	10

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

Sex; 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
	Day(s) Relative to S	tart Date	3.1. 4 /	5.04.5	0.00,00	
Terminal		Mean	229.2	225.6	236.3	233.8
BW		SD	22.3	22.7	14.5	11.9
(g)		N	10	10	10	10
Adrenal	-	Mean	ال 0.0717	0.0713	0.0664	0.0737
Glands Wt		SD	0.0067	0.0089	0.0092	0.0093
(g)		N	10	10	10	10
Brain	-	Mean	יו 2,007	1.976	2.046	2.021
Wt (g)		SD	0.093	0.099	0.077	0.049
(9)		N	10	10	10	10
Heart		Mean	ا 0.840	0.830	0.850	0.848
Wt		SD	0.092	0.057	0.034	0.065
(g)		N	10	10	10	10
Kidneys	•	Mean	יו 1.752	1,820	1.769	1.815
Wt (g)		SD	0.164	0.177	0.140	0,101
19)		N	10	10	10	10
Liver		Mean	7. t56 l'	7.636	7.338	7.763
Wt (g)		SĐ	0.720	1.037	0.512	0.548
		N	10	10	10	10
Overies with	-	Mean	0,1309 11	0.1272	0.1231	0.1364
Oviducts Wit (g)		SD	0.0173	0.0172	0.0143	0.0150
		N	10	10	10	10
Spleen	•	Mean	0.498 11	0.518	0.507	0.513
Wt (g)	-	SD	0.089	0,119	9.068	0.060
		N	10	10	10	10
Thymus	•	Mean	0.4343 1	0.4654	0.4762	0.5218
Wt (g)		SD	0.0998	0.0741	0.0967	0.1127
		N,	10	10	10	10
Uterus	-	Mean	0.727 R ²	0.457 dd ²	0.615	0.490 €
Wt (g)		SD	0.247	0.061	0.276	0.057
18/		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 RATIOS¹

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			0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
	Day(s) Relative to S	tart Date	-	·		
Adrenal	•	Mean	0.1781 11	0.1766	0.1540	0.1773
/TBW (Ratio)		SD	0.0165	0.0328	0.0253	0.0264
(Nauo)		N	10	10	10	10
Brain	-	Mean	5.846 11	5.766	5.722	5.682
/TBW (Ratio)		SD	0.411	0.355	0.497	0.294
(Rato)		N	10	10	10	10
Epididymides		Mean	2.8075 11	2,9351	2.7030	2.6712
/TBW (Ratio)		SD	0.2682	0.3125	0.3143	0.3544
(Natio)		N	10	10	10	10
Heart		Mean	3.251 U	3.362	3.315	3.214
/TBW		SD	0.151	0.151	0.128	0.149
(Rato)		N	10	10	10	10
Kidneys		Mean	7.184 !!	7.199	7.274	7.387
/TBW		SD	0.610	0.541	0.421	0.560
(Ratio)		N	10	10	10	10
Liver	•	Mean	30.549 R²	30.052	31.962	31.893
/TBW (Ratio)		SD	4.348	1.405	2.654	3,559
(1,800)		N	10	10	10	10
Spleen	•	Méan	2.256 11	2.199	2.012	2.139
/TBW (Ratio)		SD	0.255	0.391	0.184	0.312
(Natio)		N	10	10	10	10
Testes	-	Mean	8.549 (1	9,108	8.564	8,657
/TBW (Ratio)		SD	1.201	0.971	0,970	0.885
(USRO)		N	10	10	10	10
Thymus	-	Mean	1,4134 F	1.5209	1,4171	1.3939
/TBW (Ratio)		SD	0.4037	0.3105	0.2319	0.2919
(Nauv)		N N	10	10	10	10

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

Sex: 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
	Day(s) Relative to S	tert Date	·	·		·
Adrenal	•	Mean	יו 0.3139	0.3168	0.2812	0.3157
/TBW (Ratio)		SD	0.0265	0.0336	0.0372	0.0399
(Nauu)		N	10	10	10	10
Brain	-	Mean	8.801 li	8.828	8.692	8,664
/TBW (Ratio)		\$D	0.545	0.852	0.686	0.492
(Nauu)		N	10	10	10	10
Heart	-	Mean	3.665 11	3,692	3.605	3.625
/TBW (Ratio)		SD	0.189	0.171	0.178	0.163
(izaco)		N	10	10	10	10
Kidneys	-	Mean	7.657 11	8.094	7.505	7.783
/TBW (Ratio)		SD	0.412	0.639	0.657	0.602
(Nauv)		N	10	10	10	10
Liver	-	Mean	31.278 11	33.819	31.158	33.269
/TBW (Ratio)		SD	2.212	2.693	2.883	2.772
(MBIO)		N	10	10	10	10
Ovaries with	•	Mean	0.5727 11	0.5635	0.5222	0,5835
oviducts/TBW (Ratio)		SD	0.0669	0.0474	0.0643	0,0581
(USIO)		N	10	10	10	10
Spleen	•	Mean	2171 11	2.284	2.149	2.191
/TBW (Ratio)		SD	0.300	0.384	0.291	0.206
(Izano)		N	10	10	10	10
Thymus	-	Mean	1.8863 וי	2.0742	2.0184	2.2362
/TBW (Ratio)		SD	0.3463	0.3287	0.4057	0.4918
(Lend)		N	10	10	10	10
Uterus	-	Mean	3.159 2	2.060 DD	2.579	2.103 _{DI}
/TBW (Ratio)		SD	0.949	0.452	1.063	0.277
(vano)		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 RATIOS¹

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		0 mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Group 3	1536 mg/kg/day Group 4
	Day(s) Relative to Start Date				
Adrenal	- Mean	0.0306 11	0.0307	0.0270	0.0312
/BrW (Ratio)	SD	0.0031	0.0056	0.0043	0.0039
(read)	l N	10	10	10	10
Epididymides	 Mean 	0.4813 11	0.5095	0.4738	0.4700
/BrW (Ratio)	SD	0.0465	0.0535	0.0521	0.0573
(Lyano)	l N	10	10	10	10
Heart	• Mean	0.558 R2	0.585	0.583	0.566
/BrW (Ratio)	SD	0.038	0.048	0.052	0.027
(Maud)	N	10	10	10	10
Kidneys	· Mean	1.232 1	1.251	1.278	1.300
/BrW (Ratio)	SD	0.114	0.100	0.114	0.078
(Mauo)	N	10	10	10	19
Liver	- Mean	5.238 (*)	5.228	5.633	5.614
/BrW (Ratio)	SD	0.727	0.374	0.740	0.579
(reno)	N	10	10	10	10
Spleen	- Mean	0.38B II	0,380	0.353	0.376
/8rW (Ratio)	SD	0.057	0.055	0.039	0.044
	N N	10	10	10	10
Testes	• Mean	1.469	1.581	1.498	1.523
/BrW (Ratio)	SD	0.235	0.155	0.123	0.125
	N	10	10	10	10
Thymus	• Mean	0.2436 11	0.2630	0.2502	0.2450
/BrW (Ratio)	SD	0.0739	0.0472	0.0514	0.0476
(rund)	N	10	10	10	10

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

Sex: 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
	Day(s) Relative to Sta	art Date				
Adrenal	•	Mean	יו 0.0357	0,0361	0.0325	0.0365
/8rW		SD	0.0024	0.0043	0.0047	0.0050
(Ratio)		N	10	10	10	10
Heart	-	Mean	0.418	0,420	0.416	0.420
/BrW		SD	0.031	0.028	0.026	0.036
(Ratio)		N	10	10	10	10
Kidneys	-	Mean	0.872 11	0.920	0.866	0.898
W18/		SD	0.056	0.062	0.080	0.049
(Ratio)		N	10	10	10	10
Liver		Mean	3.566 11	3.862	3.592	3.842
/8rW		SD	0.325	0.476	0.310	0.267
(Ratio)		N	10	10	10	10
Ovaries with	-	Mean	0.0652 11	0.0644	0.0603	0.0676
oviducts/BrW (Ratio)		SD	0.0075	0.0086	0.0079	0.0078
(Legary)		N	10	10	10	10
Spleen	•	Mean	0.248 11	0.261	0.248	0.254
/BrW (Ratio)		SD	0.039	0.054	0.035	0,031
(Leano)	1	N	10	10	10	10
Thymus	•	Mean	0.2158 1	0.2366	0.2332	0.2583
/BrW (Ratio)		SD	0.0459	0.0434	0.0489	0.0561
(nauv)		N.	10	10	10	10
Uterus	•	Mean	0.361 R²	0.232 dd3	0.301	0.242 d
/BrW (Ratio)		SD	0.11B	0.033	0,136	0.028
(read)		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

28-Day dietary Study in rats Protocol # P703.01 IMP PSI, ID: 160726-5R Study No: 43166

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

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

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 Chosapeake Dr. Redwood City, CA 94063

8. SPONSOR REPRESENTATIVE

Rachel Fraser Impossible Foods, inc. 525 Chesapeake Dr. Redwoud 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.

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

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.

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

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 Animals⁴. 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 $21 \pm 2^{\circ}$ 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 tibitum 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 tibitum 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 Toklad, Madison, Wl. 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.

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

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 Monet 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)	Dictary Dose Level/ Target Exposure of Test Substance* (mg/kg/day)
ı	10/10	0	0
2	10/10	250	512
3	10/10	500	1024
4	10/10	750	1536

^{*}Bused on 48.82% active ingredient (A). Say Leghamoglobin) of Say Leghemoglobin Preparation to # PP-PGM2-14-088-301

10.E Justification of Dose Level Selection

The Sponsor, in consultation with the Study Director, and based on a 14-day palatability/toxicity study (43167¹) 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 Laba (2016). Soy Leghemoglobin Preparation, Parifized Soy Leghemoglobin Preparation and Bovine Eryphrocytes: A 14-day dietary toxicity/putatability study in rats (In Druft).

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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 next 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

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from the middle of the mixer only. Chemical analysis will verify the diets as bomogeneous 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.

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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 indirect, silt-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 precedures 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 text substance, and approximately weekly thereafter, a detailed observation will be conducted (PSL SOP #726) white handling the animal, generally on days that the animals are weighted and food consumption measurements are taken. Potential signs noted should include, but not be limited to changes in skin, fur, eyes, and monous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, pilocrection, pupil size, unusual respiratory pattern). Likewise, changes in gait, posture and response to handling as well as the presence of cloude at tooic movements, stereotypes (e.g., excessive grooming, repetitive circling), or bitarre behavior (e.g., self-mutilation, walking backwards) should also be recorded. The date and clock time of all observations ant/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 outlineasis 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 Galu

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 \pm 1). Decedents need not be weighted. Body weight gain will be calculated for selected intervals and for the study overall.

11.67 Food Consumption, Food Efficiency, and Dictary 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.

II.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 dusing 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 K₂EDTA 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

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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) hemaglobin concentration (HGB)
hematocrit (HCT) mean corpuscular volume (MCV)
mean corpuscular hemaglobin (MCH) rod 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) scrivated partial thromboplastin time (APTT)

11.H.3 Clinical chemistry: Will include:

serum aspartate amino transferase (AST)
sorbitol dehydrogenase (SDH)
total bilirubin (BILI)
blood creatinine (CREA)
triglycerides (TRIG)
total serum protein (TP)
globulin (GLOB)
inorganic phosphorus (IPHS)
potassium (K)

serum alanine aminotransferase (ALT) alkaline phosphatase (ALKP) urea nitrogen (BUN) total cholesterol (CHOL) fasting glucose (GLUC) albumin (ALB) calcium (CALC) sodium (NA) chloride (CL)

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11.H.4 Urinalysis: Will include:

quality (QUAL) color (COL) glucose (UGLC) clarity (CLAR) specific gravity (SG) volume (UVOL) protein (UMTP)

ketone (KET) bilimbin (UBIL) blood (BLD) 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.

Terminal Sacrifice and Histopathology

11.1.1 Scheduled Sacrifice

At terminal sacrifice, all survivors will be euthanized by exsanguination from the abdominal aorta under isoflurane anesthesia. Ali 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 thymus ovaries with oviduets (combined) epididymides (combined) pterus

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 ileum with Peyer's patches (prostate and seminal vesicles) salivary glands (sublingual [e]unum adrenals kidneys submandibular, and all gross lesions larynx parotid) liver skeletal muscle aorta bone (femur) lungs bone marrow (from femur & lymph node mandibular spinal cord - 3 levels: lymph node mesenteric cervical, mid-thoracic, sternum) and lumbar brain - 3 sections including mammary gland medulla/pons, cerebellar, nasal turbinates solera and cerebral cortex stemum cecum ovariet stomach CETVIX oviducts thymus colon panereas thyroid สีขอสัตกบอ parathyroid trachea esophagus peripheral nerve (sciatic) urinary bladder Harderian gland DÜRTYRX ulenis heart pituitary gland vagina

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

cyes epididymides

uptic sterve

textes

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

11.1.2 Unscheduled Sacrifice

Any ret that does 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. Rata will be evaluated for gross lesions. Organs and tissues will be excised, weighted (except for animals found dead), and preserved as described for those unimals secrificed 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 selections 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 cosin (HE) and examined by light microscopy. Additional special stains can be added based on HB 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 (lu-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 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. Dunnen's test)^{2,3}. Where variance is considered significantly

¹ Harded, MS. (1937). Properties of sufficiency and analysical lesse. Proceedings of the Royal Statistical Society Series A, 160, 268-282.

Dunnett, C.W. (1964). New trailer for multiple companions with a control. Biomenics, 20(3), 482-491.

^{*} Domact, C.W. (1980). Pairwise multiple compactsons in the unequal variance case. J. Awter. Station, Acres., 75, 795-800.

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

If warranted by sufficient group sizes, the incidence of clinical observations may be evaluated through sequential application of a trend test³. 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^{IM} version 8, Tables and Statistics, Instem LSS, Staffordshire UK).

	Method of Statistical Analysis		Statistical Analysis
Parameter	Preliminary Test	if preliminary test is not significant	If proliminary test is significant
Clinical Pathology*	Levene's test for bornogeneity and Shapiro-Wilk test for pormulity	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 lass than a certain value, calculations are performed on half the recorded value. For example, if bitirubin is reported as <0.1, 0.05 is used for any calculations performed with that bitirubin 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 mothods 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;

Kruskal, W.H., & Wallia, W.A. (1952). Use of ranks in one-cellerion variance analysis. J. Amer. Statist. Acros., 47, 583-621.

Duon, O.J. (1964). Multiple contrasts using rank scans. Technometrics, 6, 241-252.
 Agresti, A (2013). Categorical Data Analysis (3rd Edition). John Wiley & Sore, Inc. Hoboken, NJ.

Agreed, H. (1960). Robust tests for equality of variances In: I. Olkin et al (Eds), Contributions to probability and statistics (pp. 278-292), Psio Alio, CA: Stanford University Press.

Shapiro, S.S. & Wilk, M.B. (1965). An analysis of variance test for example (complete samples). Biometrika, 52(3-4), 591-611.

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- 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.1: Denise Hoban, BA, MLT, ASCP

Clinical pathology evaluation

Product Safety Labs 2394 US Highway 130 Dayton, NJ 08810

P.J.: Odete Mendes, DVM, PhD, DACVP, DABT

Test substance and dictary 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.J. (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

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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 Disposition Test substance analysis

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

Receipt, date of birth Initial health assessment Clinical observations Histopathology data

initial health assessme Dosing

Individual necropsy records

Body weights

Organ weights

Food consumption

Ophthaimologic 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 Chesapoake 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 recoipt, unless otherwise specified by the Sponsor. All remaining test substance will be returned to the Sponsor unless otherwise directed.

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

19.	PROTOCOL APPROVAL	(b) (6)	
	(b) (6)		
	Signature:	Signature:	
	Rachel Fraser, PhD	Mithila Shitut, BVSc & AH, MS	
	Sponsor Representative	Study Director	
	Impossible Foods, Inc.	Product Safety Labs	
	Date: 9/16/11/0	Date: 9 21 1C	_
	(b) (6)		
	Signature:		
	Odete Mendes, DVM, PhD, DACVP, DABT		
	Director of Toxicology and Pathology		
	Product Safety Labs		
	Date: 16 de 16		
	Date. 10 dely 10		
20.	PROTOCOL REVIEW-		
	Signature:		
	Rhonda S. Krick, BS		
	Quality Assurance Director		
	Product Safety Labs		
	Date: Sepile, Doll		
	value.		

New Issue: 09/16/16

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)

Mithila Shitut, BVSc & AH, MS Study Director Product Safety Labs 9/28/16

Date

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 Laboratorics (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 Elizaheth 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)

Mithita Shitut, BVSc & AH, MS

Study Director Product Safety Labs 12/23/16

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

Tune 1 2017

Date

PROTOCOL SECTION: 11.1

Add to section 11.I.

11.1.4 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

APPENDIX B: FEED, WATER, AND SEROLOGY ANALYSES

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

APPENDIX B (cont.): FEED





++++ ENVIGO

Teklad Certified Global 16% Protein Rodent Diet

 Lot Number
 2016C-080216MA

 Date of Manufacture
 08/02/16

 Report Date
 08/18/16

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)

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

(b) (6)

I have reviewed this document 2016.08.16 12:37:20 -05'00'

Analysia	Result (%)
Company of the Company	ALC: NO
Protein	16.40
Fat	3.83
Fiber	2.96
Moisture	10.33
Ash	4.74
Calcium	0.94
Phosphorus	0.63

	i Cipi ino 45 45		
Annlysta	Result	Umis	Established Maximum Concentration
History Mesera			
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
Myctioxin	1000		
Affatoxin B1, B2, G1, G2	< 5.00	ррь	5.00
enganerak presentere			
Aldrin	< 0.01	ppm	0.03
Lindane	< 0.01	ppm	0.05
Chlordane	< 0.01	ppm	0.05
ODT & related substances	< 0.03	ppm	0.15
Oieldrin	< 0.02	ppm	0.03
Enstrin	< 0.02	ppm	0.03
Haplachior	< 0.01	ppm	0.03
Heptachlor Epoxide	< 0.01	ppm	0.03
Toxaphene	< 0.10	ppm	0.15
PCBs	< 0.10	ppm	0.15
a-BHC	< 0.01	ppm	0.05
6-BHC	< 0.01	ppm	0.05
d-SHC	< 0.01	ppm	0.05
Hexachlorobenzene	< 0.01	ppm	0.03
Mirox	< 0.01	ppm	0.02
Methoxychiar	< 0.05	ppm	0.50
Segundo de Constante			
Thimel	< 0.15	ppm	¢ 0.50
Diazinon	< 0.14	ppm	0.50
Disulfaton	< 0.15	ppm	0.50
Methyl Parathion	€ 0.14	ppm	0.60
Malethion	< 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
Present Glasses Class as an order rest of Changes 4: Erroge Str. L.			

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.

CERTIFICATE OF ANALYSIS

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

Date : 6/28/2016

CV3 CIPDOUL	F 7 10-3141								Mepors Deck	of well to se
PAS Savrybu RD	Client 90	Analysis	Azsults	Limits	PQL	MICA	MAG.	Method	Date Sampled	Cate Assiyzed
P16-3141-01	Room #7	Соррег	MD	mg/L	0.05	0.0185	1.30	5M 3\$12 B	6/21/16 11:20	6/27/16 15:13
P16-3141-01	Room #7	Zinc	NO NO	mt/l	0.025	0.0092	5.00	SM 3211 B	6/21/16 11:20	6/28/16 15:34
P16-3141-01	floom #7	lead	NO	mu/L	0.002	0.000462	0.00\$	SM 3113 8	6/21/16 11:20	6/23/16 15:15
P16-3141-01	Room #7	£. Coh / Colifert	Abtent	Pres/Abi	1 Col/100mL	1 Coi/100mL	0 CoV100m2	SM 9223 B	6/21/16 11:20	6/21/36 16:55
P16-3141 O1	Ream #7	Total Coliform / Collect	Absent	Pres/Abs	1 Col/160mL	1 Col/100mL	O COLUZOOME	SAN 9223 B	6/21/16 11:20	6/21/16 16:55
P16-3141-02	Room #10	Copper	HS	mg/L	0.05	0.0185	1,30	SM 3111 B	6/21/15 11:25	6/27/16 16:35
P16-3141-07	Room #10	73nc	ND	mg/L	0.025	0.0097	5.00	SM 3111 8	6/21/16 11:25	6/23/36 13:31
P16-3141-02	Roam #10	Lend	MD	me/t	0.003	0,000462	0.005	SM 3113 8	6/21/16 11:25	6/23/16 15:19
P16-3141-02	Room #10	E. CoG / Colifert	Absent	Pres/Abs	1 CoV100mL	1 Col/100mL	0 Coi/100mL	SM 9223 B	6/21/16 11:25	5/21/16 16:55
P16-3141-03	Anom #10	Total Coliform / Colifert	Absent	Pres/Abs	1 Col/100mL	1 Col/100mL	0 CN\\100m{	SM 9223 8	6/21/16 11:25	6/22/16 16:53
P26-3141-03	Acom #29, Pressure Station	Copper	NO	me/L	0.05	0.0185	1.30	5M31116	6/21/16 11:35	5/27/16 16:38
P16-3141-03	Room #29, Pressure Station	Zinc	N/D	mg/L	0.025	0.0092	5.00	5M 3111 B	6/21/16 11:35	6/28/16 13:39
P16-3141-03	Room #29, Pressure Station	Lred	**0	meA	0.002	0.000462	0.005	SM 3213 B	6/21/16 11:35	6/73/16 15:24
P16-3141-03	Room #29, Pressure Station	E. Coli / Colifert	Absent	Pres/Abs	1 Col/100ml	1 Col/300ml	0 Col/100mi	SM 9223 B	6/21/16 11:35	6/21/15 16:53
P16-3141-03	Room #29, Pressure Station	Total Coliform / Colliers	Absent	Pres/Abn	1 Col/100ml	1 Col/100mil	0 Cel/100mi.	SM 9223 B	6/21/16 15:35	6/21/16 16:55
P15-3141-04	Sipper Battle	Total Colliform	NG	Col/100mL	1 Col/100mL	1 Col/100mL	0 50\/100mL	SAA 9222 B	6/21/16 11:40	6/22/16 11:10
P16-3141-05	Sipper Tap	Total Californ	AC Interference ***	Col/100mt	1 Col/100mL	1 Col/100ml	0 Cal/100mL	SM 9222 B	6/21/16 11:40	6/22/16 11:20

(i) SCP 508 DEV tosting not respected on Si prestip (In 7/0/10)

(i) Cm 13 fewest not analyzed due to room being out of service (b) 7/7/10

Aminals are a longer given water from unfilter source (Nowedstrom)
Missing Sampling of econ 13 has no impact.

Sipper bottle basted OK, no need to test sipper top (tube)

7/7/16

184

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.



FINAL REPORT OF LABORATORY EXAMINATION

4011 Discovery Drive, Columbia, MO 65201 1-800-869-0825 1-573-499-5700

ideoobloresearch@ideoc.com

www.idexorbionesearch.com

IDEXX BioResearch Case # 30789-2016

Received: 11/15/2016 Completed: 11/16/2018

Submitted By

Mithila Shitut

Phone: 732-438-5100 ext. 1558

Product Safety Labs

Email: MithilaShitut@productsafetylabs.com

2394 US Highway 130 Dayton, NJ 08810

Specimen Description

Species: rat

Purchase Order #: P1602593UDC1

Description: Opti-Spot strip(s)

Number of Specimens/Animals: 3

Cherc ID	Privestigator	Roem ≠	Stram (Breed	Sex	Ago Study Number
257M 10.28.16	Mittile Shout	15	COYCRL	M 3m	43166
288M 10,28.16	Akihila Shaut	15	COYCRL	M 3m	43166
316F 10.28.16	Alithita Shitut	15	CO/CRL	₹ 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.

8 you have questions, obstate call our toll free number at 1-800-869-0825 or e-mež us at ideal-boresearch@detx.com.

**DEXX BioResearch Case # 36789-2016

Page 1 of 2

SEROLOGY SUMMARY

	257M :	0 26 16	269M	10 28 16	: 316F	10 28,16
RPV				_	1	•
	4				• • • • • • • • • • • • • • • • • • • •	
RMV		•	į	•		-
in common ancient makes an in the artists of the	*		j			
KRV	- : ·		}		:	-
to accept a secondary of the contract of			4		i	
H1			į.	•		-
RCV/SDAY			,	•	i	•
recorded to the contract of th			4			
RTV		•		-	i	-
Rut IgG		•		N	<u>.</u>	N

Lagend: ** positive - * negative blank = test not performed EQ = equivocal HE = hemolysis precluded testing 1 = insufficient W = week positive WB = Western Biol confirmatory analysis pending NS = non-specific reactivity N = normal tyG L = test than normal tyG

Page 2 of 2 IDEXX BioResearch Case # 36789-2016



FINAL REPORT OF LABORATORY EXAMINATION 4011 Discovery Drive, Columbia, MO 65201 1-800-669-0825 1-673-499-5700

idexochioresearch@idexoc.com

www.idexxbioresearch.com

IDEXX BioResearch Case # 30789-2016

Received: 11/15/2016 Completed: 11/16/2018

SEROLOGY DETAILS

Page 1 of 1

	Вазаиле	2571	10.28.16	268M 10/28/16	316F 10 79.16
tore			- ,	Style St	is i.e. i
RPV purited virus	MF1 > 2,000				•
NS1 ¹	MFI > 3.750		•	•	•
RUN	150				ran Marin (Arrament (Arrament
RMV VP2 recombinent	MF1 > 2.000		•		
NS1 ¹	MFI > 3.750		•	· •	
KKV.	A Particular and American Control of the Control of		ranga Tangga		
KRV punited virus	MF1 > 2.500		-	•	
NS1 ¹	MFI > 3.750	,	•	_	-
RI	- 17. 17. 1 - 17. 17. 1		And the second second	engangan da in industria. Na	
H1 purified virus	MF1 > 1,750	es-y	•	*	•
NS1 [†]	MF1 > 3.750	•		·	
RCV/8DAV	er en				- The second second of
RCV/SDAV purified virus	MF1 > 3.750	/.	• **	•	
RCV/SDAV Spike	MFI > 3.75D		•	•	-
RTV			andreas and armost	t in man said. Said All Said	
RTV purified virus	MF1 > 2.000	E 1140-14-15-0	· · · · · · · · · · · · · · · · · · ·	پاغىنىدىداد دادەد دەخلا ئ	-
TMEV purified virus	MF1 > 2.000		-	•	

NS1³: NS1 protein is highly conserved among rodent pervoviruses and thus serves as a generic assay for pervovirus seroconversion.

Legend: += possive -= negative blank = test not performed EQ = equinocal HE + hemolysis produided testing != insufficient W = weak positive WB = Western Bot confirmatory analysis pending NS = non-specific reactivity N = normal tgQ L + test than normal tgQ. 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 cost our zell free number of 1-800-869-0828 or e-mail us at identificroeenth@itexu.com.

IDEXX 6xxResearch Case # 30739-2016

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:

| Date | Continuous | Continuous

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 LISA 732-438-5108 psi@productsafesylabs.com www.productsafesylabs.com

APPENDIX D: CHEMICAL ANALYSIS

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

Project Title:

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

<u>Sponsor</u> 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

Page 1 of 35

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:	Date: 12/7/2016
Name of Signer: Pavel A. Aronov, PhD	
Name of Company: Impossible Foods	

Page 2 of 35 Analytical Report Study Number IF 43166

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)	12/7/2016
Pavel A. Aronov, PhD Principal Scientist Impossible Foods	Date

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STUDY INFORMATION

Protocol No.: IF-43166

Test Substance: Soy Leghemoglobin Preparation 1.03/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 PSI. 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

NTIA NTIA NTIA

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

SA0 IA 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 HA MA	SA10 27A MZ
SA0 2A MA	SA7 18A MA	SAO 7A FE
SA4 9A MA	SA10 25A MA	SA4 17A FE
SA7 16A MA	SAO 5A FE	SA7 21A FE
SA 10 23A MA	SA4 12A FE	SA10 28A FE
SA03A FE	SA7 19A FE	
SA4 10A FE	SA 10 26A FE	

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

HO LA M BO	HO H A T FE
HO 2 A T MA	HO 12 A M FE
HO 3 A M MA	HÓ 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 PE	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 IV A B FE
HO 10 A B MA	

Intermediate (Day 7) Dietary Samples for Concentration Verification:

CV LA 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. (LtN 1 - LtN 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.</p>

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

Duplicate QC stock solutions were prepared by weighing approximately 0.5 gram of a control sample (BO 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:

Calculated Conc. (mg/g) = Peak Area - Intercept Slope

Dose Cone (ppm) = <u>Cale Cone (mg/g) x Extraction Huffer Wt. (g) x 1000</u> Sample weight (g)

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

Final Cone (mg/g) - Theoretical Spike Cone (mg/g) x W1 of Sample Aliquot (g) / Final Wt (g)

% Recovery = <u>Cale, Cone, (mg/g)</u> x 100 Final Cone.(mg/g)

> Page 9 of 35 Analytical Report Study Number IF 43166

% Signal / Background ~ Avg. LIN I-A area response × 100 Avg. Control area response

% Target = Dose Cone, (ppm) / Corrected Dose Level (ppm) | x 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 ^t	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学	95.70%

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[,] final Sample - Initial Sample x 100

TABLE 1B: CHEMICAL ANALYSIS RESULTS

Results for Dietary Stability of Initial Samples

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

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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 (ppm)	Measured Concentration (ppm)	% of Target ²	Average % of Target	RSD (%)
	T(BO)	Middle	Ù	ND	NA	NA	NA
		Тор		4302	98,38%		
	2 (M)	Middle	4373	4061	92.86%	95.87%	2.92%
		Bottom		4215	96.38%	1	
		Тор		4853	103.01%		
	2 (F)	Middle	4711	4583	97.28%	98.01%	4.77%
		Bottom		4416	93.74%]
		lop		8636	98.74%		
	3 (M)	Middle	8746	8145	93.13%	95.40%	3,09%
0		Bottom		8250	94.33%		
		Тор		9669	102.62%		
	3 (F)	Middle	9422	9284	98.53%	97.71%	5.50%
		Bottom		8666	91.98%		
		Top		12226	93.20%		
	4 (M)	Middle	13118	13558	103,35%	97.85%	5.24%
		Bettom		12724	97.00%		
,		Тор		14567	103.07%		
	4 (F)	Middle	14133	14183	100.35%	98.64%	5.579
		Bottom		13072	92.49%		

NA = Not Applicable: ND = Not Detected

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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'	Group	Target Concentration (ppm)	Measured Concentration (ppm)	% of Target2
	1 (BO)	0	ND	NA NA
	2 (M)	4373	-4061	92.86%
	2 (F)	4711	4583	97.28%
\mathbf{o}_2	3 (M)	8746	8145	93.13%
	3 (F)	9422	9284	98.53%
	4(M)	13118	13558	103.35%
	4(F)	14133	14183	100.35%
	1 (80)	0	ND	NA NA
	2 (M)	6093	6158	101.06%
	2 (F)	5824	5326	91.45%
7	3 (M)	12318	12189	98.96%
	3 (F)	11664	11-408	97.81%
	4(M)	18362	19409	105.70%
	4(F)	17567	17238	98.13%
	1 (BO)	0	ND	NA
	2 (M)	7407	6906	93.24%
	2 (F)	5925	5498	92.80%
21	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

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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: HPLC OPERATING CONDITIONS

Instrument		Agilent 1100 Series HPLC System, with DAD					
Column		Waters Acquity xBridge BEH125 SEC, 7.8 x 150 mm ID 3.5p					
Flow rate (mL/min)			0.86				
Injection Volume (µl	.)	25					
Wavelength (nm)		405					
Column Temperature	·(°C)	Ambient					
Tray Temperature (°C	²)		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	()	100				
14,01-19,00 min	0.86	100	0				
19.01 to 30.00 min 0.86		0	100				

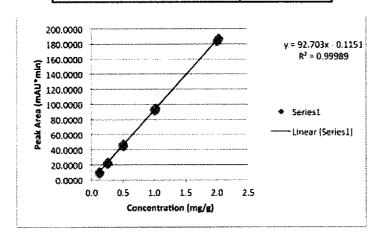
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TABLE 3: METHOD VALIDATION RESULTS

Linearity

(Analyzed on 11/17/2016)

Sample ID	Peak Area	Theoretical Concentration (mg/g)
• •	10.5743	0.1236
Lin#	10.7110	0.1239
	23,4604	0.2572
Lin 2	22,9334	0.2509
	47,5942	0.5066
Lin 3	46.4874	0.4962
11.4	94.8130	1,0224
Lin 4	93.6001	0.9964
* * =	187.6864	2,0265
Lin 5	184.2777	1.9985
	Slope:	92,7032
	Intercept:	-0.1151
Correla	tion 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
		4.1680	45,1002
	0.4962	4.1682	44.9289
LIN 3-1		4.1687	44.7097
		4.1703	44.3757
		4.1688	44.2105
Av	erage	4.1688	44.6650
ST	DEV	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)
	0.5012	45.1037	0.4878	9 7.3%	
QC	0.3012	44.9771	0.4864	97.0%	97.0%
Low	0.5062	45,4857	0.4919	97.2%	(0.3% / 0.3%)
		45.2369	0.4892	96.6%	
	1.0003	87.1050	0.9409	93.3%	
QC	1.0082	86.7802	0.9373	93.0%	92.6%
High	1 0000	86.1798	0.9309	92.3%	(0.7% / 0.8%)
	1.0086	85.6498	0.9252	91.7%	
		y = 92	.7032 - 0.115	l	

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TABLE 3 (cont.): METHOD VALIDATION RESULTS

Specificity (Analyzed on 10/17/2016)

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

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TABLE 4: NEAT TEST SUBSTANCE STABILITY ANALYSIS

Analyzed on 10/27/2016

Day	Sample Name	Sample Weight (g)	Final Conc. (mg/g)	Peak Area	Calculated Conc. (mg/g)	% Recovery	Avg. % Recovery	SD/ %RSD	
		0.1017	0,4974	45.3436	0.4738	95.25%			
0	NTIA	8490,0	0.4888	44.2652	0.4622	94,55%	94.96%	0.00367 0.38%	
		0,3011	0.4960	45,1470	0.4717	95,08%			
		0.1026	0.5017	45,6401	9,4770	95.08%			
14	NT 2 A	0.1031	0.5016	45,5543	9.4760	94.91%	95,29%	0.00537 0.55%	
		0.1008	0,4886	44.8581	0,4686	95,89%			
		0.1039	0.5087	43,0057	0.4487	88.20%			
21	NT3A	NT 3 A 0.1031	0.1031	0.5132	45,6832	0,4774	93,02%	90.88%	0.0245 / 2.70%
		0.1047	0.5181	45.3258	0.4736	91.41%			
				y = 93.1257 ·	1.2237			·	

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¹ Days relative to the initial diet preparation.

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	Samp le Vi i. (g)	Lysis Rengent Wu (g)	Dose Level (ppm)	Pesk Ares	fak. Conc. (ma/g)	Base Cone.	, (tverage (ppm)	%R50	% Yarget	% Target Average	%Turget between the atraca (Avg / RSD)			
HOLA M-1	9,5(7)	5,0400		NĐ	NA.	NA NA			NA					
10.1人がご	0,5081	50178	58	N(I)	44	NA	NA	NA	٧A	NA	NA NA			
HOLLA M-3	11.5(17)1	5.035)		NĐ	NA	NA			NA		l			
10012 A 1-1	0.3221	Sanas		#4.2142	17440	4440			101 759					
(C) 2 A T-2	0.5554	5 (9)73		42.4864	UTKN	2(4)	£80	ERE 3,049	CR01 1049	£802 3,000 95,830	62 Hz-9-	101 1461		
1602AT-3	0.5051	5/814		40,9336	0,424)	4267			97.57%		1			
BOTA M-L	0,801	4 (844)		39.6148	D-41(0)	3 4(1)		4061 1,299%	1,999.1 (Arti	1,599)%		94.029		
BODAM2	0.5299	5,9739	4375	4016607	0,4148	.977.1	4063				91233	92.99/4	45.87% 2.92%	
3003 A M-X	0.906	\$ 0660	ļ	10.639#	0.4164	4)08]	98.719]				
180 # A B-F	11,4943	3 (63)		44.17XI	ry,1470	7,50			92.98%					
HO4 A B-1	0.3022	5.045.5		b	4	3535	4215	4.99%	* 06.38%	498.00				
HOAAUA	0,5172	11621		42.4020	0.4,107	(416)			CAD 1.14.1					
19O 5 A T-1	0.5277	5,0770		47,15%)	0.4880	2095			99A97]			
BULLATO	0.5022	5.0647		47.6758	0.4012	495%	48(5)	220%	88214	160.615	1			
383.5 A T-J	13.4967	\$11401		45 A367	Urthise	290			101 134		[
MINA MI	0.3(0)	SEAS		15.7H50	0.4720	441)	arianarian a batanaria arian.		99635					
MILLO A SI-2	115150	18555	4713	AN TIED	0.5455	1130	4941	1017	च्यान्त्र	41 2995	98arcs			
BOn A M-3	0.4991	4,4870		44 9234	0.1613	3629			9H,20%	1				
110 : A H-1	11-4997	58360		43,7868	0.4517	450		T	00.64%]			
1027 A 8-2	11-150-30	1315834		4),0276	0.1170	4267	7110	1 25%	5% 91.57%	પ્રાથમ				
16) 7 A H-1	0.59134	5000		40.0629	0.4.444	4429		ĺ	24.023		1			

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 9 Conf. (110 BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

Sample III	Samp le Wt. (p)	Lytis Rengent Wt. igt	Dose Level (ppm)	Prak Arra	Cule. Conc. (mg/g)	Duse Cone. (ppm)	Average (gpm)	% HSD	% larget	% Turget Average	McTurget between the squata (Avg. / RND)
HOBAT-I	0.04	10,1502		31,3902	0.1305	64.00	:	1	79,73%	0.0	
HOBAT2	0.503	10.1210		37,2054	19,3420	687E	184	1979	78.56%	77.41%	
HOHATA	B. 127	AIROOF N	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	3.5.0665	0.1617	7120	.b5 a		WIKIK.		and the second second
HOPA Mil	03341	100177	-3%	3446040	00.00	60.65	1.20	22-17	77mt		90,45%)
HOSA M2	0.5213	10.0362	1974h	34.1460	0.7530	\$ 1773	(HEHE	4.25%	77,4 9 %	30.11%	4012
HUYA M-3	11.5177	103,004	3.825	36,7414	033772	7,9122	19 14 14 L	in the second	83.49%	The Control	#100°A
390 10 A 0-1	95118	10.3798	100	.37/2761	0.4852	7625			107.10%	the second	ega lina in a
HOUSE BE	0.4921	100637		.M.3183	(13.731)	7607	7135	TOUR	27.207	94.1799	
HOIOKBA	0.500	10,7426	rejaro at	343700	0.3502	57.54	12 H 14		77.23%	by Color May 1	
HOSTATA	D,1975	10.1086	Leanner of	39,6039	0,4093	E133	3-1 1 100	. 1955 ·	RELAGE.	The State of	er i gelejgilag
HO HATE	U.4(104	(0079)			().ext5	8002	gyin:	4.67%	N3.N8%	W) (29	
KITATS	0.1020	100604	78.1	44.06Ni	D.4546	9030	199	3 3	96,021%	12 1 XXV	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Shi ta A Sail	0.5Z23	10,0024		N/6492	0.4500	\$ 5078	***************************************	1	92.10%	-1,1	ويستشد
9012AM2	0,4906	10048	9822	418,3411	0.4148	1 (535	842	3,70%	(4).59%	10.416	8735781 443.5
183 12 A SEJ	03129	ionitt		39,873	0.4[2]	970 T	w. G	10.10	8502%	100	14.
HO 13 A 8-1	0.5200	10.0188		41,4060	0.4276	£2.50		78(%) \$383%	87,44%	Service Laboratoria	
HU JAH 2	0.7021	IDRAT7	100 C	1X.2D93	13,17652	\$ 7912	7K%		43.9H4 #1,1993	M1,199	
MODABS.	Ø.5000	IOOF46	Zaus	19.6744	(4,164)	79.17		Company (Co.)	**************************************	,	A part of the control of the control
BULLA T-I	11,5172	15.0007	1.00	30.1873	13,11999	S. BULF	against green		FREIGH.	11 to 11 15 15 15 15 15 15 15 15 15 15 15 15	
HOTHAT 2	0.5146	15 1351	10 mg/m/	34/3(0)	(A.553)	1(1528	677	TAUN	80.25%	24.34%	
HO-FAAT.3	0.5112	150063	3.376	32,2394	0.1119	9782	Sec. 3 12	10 Met 2	74.57%		13 KB 12 S
HELES A MAT	03150	15.1496	Sant S	3324490	0.1-265	10028	1644		11.02	ine constant	-4500
HO 15 A N-2	0.3113	150106	13118	M.2383	(3.1920	(0)98	10364	0.681%	70,104	14.91R	7751708
EMARION	DAME	152133	Se."	32,4413	0.1339	1 10211		P	77.84TE		35735
IK) IOA B-1	65083	150000	SAME - 1	33.7001	0.1472	3 1000	Sa 5. 75	5.	78.24%	DA 1881	1、安全。12分H
HO 14 A B 2	154012	13.1201	554	32,6994	0.1366	LCO6Z	10417	(20%	78.99%	945	
HOIGABA	(1327)	152106	Sec. 30.45	35,4260.	().4630	idean		Company of the Compan	SCHOOL.	A. C. 177	

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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 10	Sample Wil.(g)	Lyxis Reagont WL (g)	Date Level (ppm)	Pesk Area	Cale, Conc. (mg/g)	Dove Conc. (ppm)	tverage (ppm)	%RSD	% Farget	% Target Average	%Target been ven the steats
HQ 17 A X-1	0.5272	150543	Arriff Garage	18,2878	0.3960	(1) 529	15 N.S.	Selvi.	81,333	i ang a jawa "	Commercial Commercial
HO 17 A T-2	0.3150	145014	E. Service	38,3201	0.9951	11:29	11384	2214	81.5%	202.0k	
HOR7ATS	0.4937	1.52(074)		35,3673	0,3664	11093	Provide a	· * · · · · · · · · · · · · · · · · · ·	78.09%	8 48 W	
HO 18 A M 1	95256	L51448	gater pera	J0.6023	0378	11357	140,20	500	78.94%	3. \$254771 S	Charlet Car
S MABE OH	G-5000	15.1290	14133	14.570N	(4,157.9	19890	11197	147%	76635	74.23%	*****
CHABI (H	0.2911	153299		10.1798	CLJ17017	11404			M2 1174		
HÚ PABI	05912	15.1035	1917	(8.9280	0.4025	11892	10.1 201	84.1574	M4 1470	uvê Gilê 💮 🤞	
1X1 19 A 8 2	0.5004	15.0729		34.5200	0.3578	(11) (82)	1034	6.89	76.VJ%	THEFT	
HOIVABO	0.4928	150028		33,33%1	03438	10543	24.6	200 A S. C	74,499	and the state of the	

NA - Not Applicable: ND - Not Detected

Cells shaded in gray were re-analyzed on 11/8/2016 and 11/9/2016 due to low signal.

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^{*} Excluded due to non-trending result

TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day B Preparation (BC) MA Analyzed on 11/8/2016, 110 FE Analyzed on 11/9/2016)

Sample ID	Samuel e Wit. IRI	Lycie Respont WL (g)	llow Level (ppm)	Pruk Aren	Fate-Coor, (mg/g)	Dave Conc. (ppm)	Average (ppm)	# RND	क Target	ti tuga Assaga	St Furgot between the strate (Avg. RSII)
HURAT-I	11,5143	10) 1/502		41,5494	D.4.K99	[9 57]	H036	5000	QU 49	48,745	
HOBATA	0.507	1D 1210		43.1624	0.430)	913-29			103,493		
H18871	0.3127	11) (34) [5		tij Ostal	0.4(6)	81X 7			YAM13		
IM APOR	0.3581	(0(477		41.6206	0.4398	8118	163.45		95.113		ila man.
HO9 A 13.2	113212	MEHAZ	1974n	39.544	6.1033	77 3 %		1.40%	XV 174.	स्ट १४%	254.1 574.1
ER AUCH	0.5177	10.13/14		41.1521	1).42504	K390			95.93%		
HO HO A B I	03110	10.3258		#1.24 % 4	0,429	8507	832 1	Time	47.3/9		
HO DA BE	RAV21	STADLE)		41,3775	0.4390	8702			300.30%		
ERAM ON	0.3239	10.1406		MARG	0.3996	7663			87.62%		
BH14 (4)	13,4544	(i) Inett		ध्री ५मान	1),1745	d/dk	1966	T	HIZRIG	1(0,42%	487 731% - 5.5875
HYTCI A T-2	(3.5054	10 (0792	4227	41.585	0.A.V02	103.49		\$.19%	V7.00%		
HOUTA E-S	BARK.	103004		N(300)	0.5[1]	(0)(4)		l	11863941		
MITZAM E	0.5222	lik(n) 34		47.0973	0.4926	010.5	AZMT	Ţ	100343	प्रश्नुस्थाः प्रश्नुस्थाः	
KUSAMI	0.4436	10)(6148		1136X48	D 43734	4121		124%	ces inn.		
K112 A M-3	0.3120	11)(4)33		43.7416	04.50	HO!K			918.5		
HO DARI	0.5.00	10.0188		14 8412 14 8412	0.494	4523	Notio	1177%	95.783		
HOLLYA H-2	0.301	HYCESTA.		4) 1711	0.4300	H. FAIN			V(193		
BO 13 A B-3	11.3066	H) QNO		40,5155	D.4.222	KIRS			\$4.60 kg		
HOMATI	11.51713	CAGOOY		2),3516	0.4202	13235		7.06%	91214	iai ars	110(125°4 1
HIBAATA	0.5146	15.135E		45.5743	U.4764	45704)	13280		1117.269.		
HUHATA	83152	13000		£1.7944	0.4372	1,1474			יויבל 201		
HO IS A MI	0.5116	15.1496		44.9781	D, ley(ei	1.9912		2.21%	104/16/5	K0,335	
K) 15 A 58-2	0.5113	120748	9418	40,7394	0.4.46	1744	1,7558		100.453		
K315 A 553	114942	15 11 12		41 7757	04335	13517	i	l	301.50%		auart.
ROBABI	11 11K1	15/00/09	į į	10,9314	9.4364	1,764		Ī	ዓትፒት ድ		
IOTEAH 2	11/1/12	ES 1231		UL(F*A)	15 41 77	12940	12724	11,95%	U1017.	the fores	
ROTH A H 3	0,520	15.2106		41.9000	0.4377	12721	· ·		96,99%		

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 0 Com. (HO MA Analyzed on 11/8/2016, HO FE Analyzed on 11/9/2016)

Sample 10	Sample Wili (g)	Lysis Reagent WL(g)	Dose Letel (ppm)	Peak Aren	Calc. Cenc. (mg/g)	Dose Conc. (ppm)	Average (ppm)	%RSD	% Target	% Inrget Average	%Target between the strata
IRD ET A T-L	0.5(7)	15(654)		47 3580	0.500	14.485	14%7	0.32%	103.183	100,07%	(晚初1年7年57年)
IK1 (2A T.2	0.5150	14.9614	i	2,0.05	0.5021	3-4641.5			101341		
HCH TATA	(1.495)	15(079	1	142.02	() 4704	14515			100.78%		
HO 18 A M 1	03156	15.1428		20,5638	0.4914	3.44.44	(4) K 1	1719	ICC.1.5%		
HET IR A ST 2	0.930	15.1290	10130	4139	(1.4515)	1.ATTT			9R 66%		
HOURANA.	U =#311	15 12/9	1	21 0.59%	0.440	34173			(60)275		
IK) IVA B-1	05112	15 0035		41,4841	0.435	(,603)	13672	471g	(65,200%	92.39%	
180 19 A El 2	0.000	12(11.0)		41.5615	0.4132) 30(K)			92 tha		
IK) 19 A 9-1	0.4924	150228		17:15	(1.2(46)	17461			40), 16°5.		

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 10/21/2016)

Sample H3	Sample Wt. (g)	Lysis Reagent Wi. (g)	Dose Level (ppm)	Proli Area	Calc. Conc. (mg/m¥.)	Dose Come. (ppm)	Average (ppm)	76850	% Taiget	% Turget Average
35 P- 1-5-1	11,480511	4 (0.012		NJ)	NA	NA NA	NA	NA	NA	NA.
SAR LAG	8,5059	1,9964		ND	NA	NA NA			NA .	
Sale (8-3)	0.5263	4.90065		ND	NA	NA NA			NA.	
SALIAI	0.8051	51002		SD	NA	NA.	/		NA	NA
5A 4- 6 A-3	0.4905	4 (0104		ND	NA	NA NA	NA	NA.	1.4	
5.5 4. 5 5.3	0.4863	4.9995		NB	NA	NA		1	NA	
55.7-15.4-1	(1:4909)	1.0744	11	ND	NA	NA NA	NA NA	NA NA	XA	NA NA
SA 7- 15 A-2	0.5123	19.987		ND	NA	NA NA			NA.	
SA 7/13 A-3	(6.063)	192(4)		20	NA	NA.			NA !	
A 10-12 A-1	0.3283	4,9491	1	No	NA	83			NA.	
A 10- 22 A-2	0.5050	1,97,80		NU	NA	85			NA .	
A \$11- 17 A-3	11,5115	4,9702		SD	NA.	N.A			NA.	
	900 L	1000		Sec. 1		10002	447 4207	5219	200	
W. C. L. S.	2017 X 172			X33					70 T. 1	
C. C				87, 11, 17, 28		S 2007 () () () () () ()			72.30	
SA 4- 9 A-1	0,644	191%		84.740.	11,4138	4296			56.195	
8A 4- 2A-2	0.4937	1.9905		17.7EC1	0.3953	39808			91.20%	
84 L V A.J	U. NICH	1 9530		41 IVAL	114525	2020			101 213	
SA 7: 10 A-1	8.4970	4 97H1	4573	39.3(180)	11,4314	461.1	វង្គជ	2809	9406G	ugatera
SA 7- 16 A-2	19.5412.5	E 94H7		¥0712	11 421 1	3:35			95027	
54.7-10 4-)	(1.5) ?h	1938		41	11-4540	4,147			CO. 173	
A Hi 23 A-1	11,34114	3.0134		59 1195	0.466	40(4)	5966	1	93015	
CA 10- 23 A 2	0.5042	1990		Q1484	0.4024	VM()		1,56%	VI (4)	W174%
iA In- 13 A-3	0.3045	5.0001		W.9739	0.3963	5928		1	37,545	

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FT Analyzed on 10/24/2016)

Sample (1)	Sample Wt. (g)	Lysis Reagent Wil (g)	Dese Ervel	Penk Area	Calc. Conc. (mg/g)	Dase Conc. (ppm)	Ascinge (ppm)	%RSD	% Target	% Target
SA D- 1 A-1	0.53(0)	5.0218	~	46.3028	11.45%)	4697		1	99,70%	
SA 0-1 A-2	0.500	1 00%0		444.441	11 MONTH	4547	desta	1 9.44	96/11/9	985 61 18
301-10-2	0.4900	3 0HN	ĺ	4405.96	11,46.22	4663		ļ	93.71%	
SA 4 10 A 1	D DHCT	Toan		42,1142	(1441)	4524	***************************************		410.00	
SA 4-10 A-2	17.63%	4.972	Ī	41,8842	0.4395	4331	4471	174%	\$10,6g	444,4476
SA + 10 A 3	0.306	5.0280		128.96	0.4045	4500			95,69%	
SA 7 174 1	0.5(8)	5,0099	4714	42.8733	0.4930	1347		1	92.77%	
5A 7 17 A 2	0.460	33416		42.9361	ひんりが	TIGH	4468	1717	62,165	性熱學
SA 1 17 A 3	0.5296	36191		15,5214	(6478)	4556			95.355	
A 10-24A 1	0.5134	1.9318		46.1824	9,4951	4716			100.11%	
A 10- 24 A 2	POID (4	1 (488)		17,4444	(1.4×4.1)	1416	76137	5013	104,15%	ALC: SOM
SA HL 21A 3	0.4960	3.0624	L	41.7(624	6,4375	1118		1	(4.41%	
\$A 0. 4 A 1	0.7215	10. (290)		17.6733	0.7542	755%	***************************************		10,579	
58.0 48.2	0.4894	10/6000		15,4056	0,1702	7633	V-W	4.55%	1 ST 37%	45 10%
SALAA	7.51 77	10,0573		14,7130	0.3639	34,17	334-4		80.09%	44 . 10 34 (a)
MATERIA	0.4920	10.0017		10-1406	(1.4780	17.12	1 (1904 LFM)	4	98.41%	31.48.27
A 4-11 A-2	0.5278	0,0884	ACE A SA ESTA	16.1328	0.3803	13.13	36.78 ·	29.9	30.59Ks.	A\$50%
A+11.A3.	9.5143	1(X(19)\$AF	41-7-4-7	158883	63758	7364		4 8000	WI TIME	
A 7- 18 A-1	0.3121	10.0562	874 6	14:2492	0.3654	7175	Fai ja kan	4	82.01%	1 Sec. 1
A. T.: 18 A.2.	0.034	0.08,99		3777416	05950	119	2274	120%	MXXX	N3.12%
A7. 18A3	0.9901	30.0922		148172	0,3680	F210		100,000	82.90%	
A NECSALI	0.35%	10.1007		37.3867	0.7911	79(2)		40,000	199.31%	g er skriver en f
A 10-25A-2	0.5453	Pour out Duff 脚 y, part	小龙龙龙龙 (1486)	13/7/51	0.3574	20 4 019	75(8	600%	. 1964 Sc. 1.	85068
ARL 25 A.A	0.520	107.1009		38,4894	(1,4028	7824	EGNYYET:		28,10%	12,89321

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FT Analyzed on 10/21/2016)

Sample HD	Sample Wt. (g)	Lysis Reagent Wt. (g)	Dese Level (ppm)	Frak Area	Cale, Conc. (mg/g)	Dove Caue. {ppm}	Arcinge (ppm)	%HSD	% Target	% Target
5A B-5, A-15	0.4950	10.1258		38, 442	0.3938	8179		332	25.81%	
SARTAL	0.5198	10.1349		33.1850	0.1473	6771	72117	11 TP3	71.100/4	16499
SA H. S. A. J.	0.9016	10.0234		11.9203	4.3339	6671		è:	30.80%	
5A + 12 A 1	0.51 (3	10.12(0).		(H),50024	(1,4149	8(3)			36.19%	
A 4 12 A 2	0.4902	0,0008) a	30.2047	0.4311	825	8107	1.779	167 10%	45,00%
M 4- 12 A-3	0.5190	(0,1180)		39.8321	0.4020	7990		466.333	294.38%	State of the state
A.7. 19A-1	0.5260	10.0654	9422	39.8435	0.4178	7992		1-6%	81.40%	20.00
A.T: 19X:2	0.395	10,1003		37.4367	0.7925	78.49	79(0	0.77%	23 20%	43 AA8
A-1914-A	13,4968	10.0567		37.4159	(1,992)	7918		77.	Set 7502	10 X 25 X 2
A 10-24 A-1	0.4976	10.120		37.671	11,1948	8000			55-27%	134,200
A 111 25 A 2	0300	0.1127		36.7730	(1995)	1000	7010	3005	81 36%	MLZ1%
AHI MAS	D.4R00	10,1002	- 3	\$7,5669	ii.xqr	8)25		1	36.23%	
SAROAT	(74) (1)	15.1400		30.908	0.3327	9702	Market Chizalenni		74.04%	300
SAD-6A-7	0.408	150003		31,8210	(1.5)34	100033	110715	3.214	78/25%	19874
SAP GAJ	0.503.	.15:3767	gasjen de f	\$3.102N	03459	10,4040		Massa Ca	79.51%	31.000
44-13 A-1	A5146	(5,002)		34,2314	9,4637	10630	F. Ans.	E-bytes	建以除	3 4 6 A 1 B
2 A CI . L.N.	0.4011	13,1141		33,9166	4),3600	11235	11021	7.08%	303.045	MOIT
U+ 3.43	9.5149	15 1230	100000	30-H(X)	0.36906	11197			\$3.06%	4860 K. C. C. C. C.
A 1. 20 A-1:	0.5002	131839	13118	34.7194	0.363P	10680	S 18-1 S	Behavior.	87318	\$ 100 Person
A 7: 30 A 2	0.52281	15070		34,1100	(1.1567	10044	HOW	0.25%	78.079	78,36%
A3 WAS	U.AVIV	15.1021	e da in brês	ME LETA	11.0104	9903		448 M	71.10%	J. Do. 21/20
A.H. 27 A.1	0,5184	(大720)		34,0004	0.36(4	10354	12 mg 13 mg 25		例).45%	15-75, 195
A 10 27 A 2	0.9000	15(0位		12 402	0.3400	10681	FOSUS	1) TIN 81 J.35		#1749
A 10 27 A 3	0.5138	(5.(8.24)	เดากรดาดั	34,3160		10319	A mark with the	\$1588315.1 · .	28)C34(%	TENERAL.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day o Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA Ft. Analyzed on 10/24/2016)

Sumple 4D	Sample WL (g)	Lynis Rengunt W4. (g)	Dawr Earel Eppmi	Penh Ares	Calc. Coor. (mg/g)	Duse Conc. (µpm)	Average (ppm)	%RSD	% l'argei	% l'arget Average
MAR TAIL	13155	PUMP	3,44	33.8171	5344	(000)	LONG WITH	177477	70.77%	
3A 0 7A 2	0.4956	150274		32.7200	0.3423	(0380)	18175	1.28%	73.45%	72.(IPE
SA 0-7 A-3	0.5365	1.919927	# 149.81 B	33-8066	0.3538	101/41	1200	200 T	71.77%	Harris Alexander
\$A4-14 A-1	0.5104	1319934		31,6,979	D.3331	962		Carlotte St.	68.07%	Serie validadesi
844 442	1 (13/22	150737		31,9091	0.3337	9623	96/34	112%	69.30%	68.62%
S4+ I+ &3	0.4935	15.1410	624-44	301000	0.3145	0651	aid ii digar	watering .	(#.Z/Y)	AND JACON
5A 7 31 A-1	0.5144	15,1119	(4)33	31.4223	D. 3280	960		1 - A 20	68.30%	
SA 70 21 A 2	§ (1.5(T)4	15.10IT	erra in r	28.6012	D. 2000	0040	0717	7.30%	化 加	(#.76%
SAT IL AS	11.492B	(3.0646	5 16 X	32,6449	0.3421	10450	100000000000000000000000000000000000000	383678	73.99%	
\$4 10 JEA E	0.5035	150914	25 3 X T	33 1480	13,363	1412013	3 1 A 1 A 2 A 2 A 1		71.33%	The state of the s
3A 10-28 A-2	1 (1,4988	15.1463		31,2624	0/3/290	9990	9714	3.80%	70.69%	68.72%
SA HE TRAGE	£ 0.5003	13/00	A	38.1629	D.HHA	906		180.3	pr Ju	and the state of the

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-unalyzed 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 (1)	Sample We (g)	Lynes Rengent Wil. (g)	Unse Level (ppm)	Posk Area	Calc. Conc. (mg/ml.)	Pose Conc.	(ppm)	55R50	% Farget	% Targer
54 H 44 F	12.31.492	100272	gartegig kirilining	J6A329	(139/99	7710		1	191_16/E	
849-142	0.5072	(20)2)		33,7410	0.3593	?222	1600	Signa .	83.8%	97.98%
SARAAA	0.5260	ionser.		39.3634	0.47.90	8134	1. Jan. 1. Say 1. 31.	2.0	92,99%	a diskabilita
SA # IF A !	9,3166	1010/20		14,300	0.532	7249	Som Eren	Sec. 10.5	10.00	. See
5A 4-11 A-2	0.5129	10,0723	医肾份验证	36,7481	0,3071	7799	7441	4.17%	89 1674	H500%
5A 41 14 A.3	0.5193	9.9986	17.94	14.8752	03771	275	81 1 1 2 2 1 1	3.1.2.5	83.18%	
5A.7: 18A-1	0.3092	10.0570	I Control	342011	C.VITA	74.Q	in Same	12. \$26.	85.21%	1.00
MT 18A-2	0.5045	10.0593		36.1730	03910	7793	7595	235%	9913%	96406
547- 18A-3	0.5(11)	100360	Property and	33.5720	0.9945	2500			86.37	a suggested and
A III 25 A I	0.52,09	49714	F-2000	39850		35 82th	W. Carlow Se	3	93,80%	3200
A IU IS A 2	0.3084	9.9885		33 (250	0.830	752)	7647	1700	35.028	199,72%
IN ID 25 A.A.	CAPACA)	100503		3,3,9542	G.5996	TR107			2751.CH	1.7
SAILS A-I	0.4950	10 1258	1	185,034	0,4407	1,100		1	95,67%	
SA II- 5 A-2	0.5194	(0)340	1	10,0642	(1.663)	4927	un4	0274	45414	44. 34. 44
54 IL 5 A.3	0,300	10 0224	1	10,7005	0.4535	9061]	46,17%	
54 4 12 A-1	11,5179	[01-120e	Ī	19 83 14	0.454;	1909>		1	केर महर	
5A 4-12 A-2	0.4092	0.0008	i	10 181	0.4529	4574	1918	1.0993	95.13%	84 65%
54 4 12 4 1	II.MIMI	10.100		14.4964	(1.45(1)	85,45		1	95 H#	
SA 7 19 A J	0.520)	10 0654	4422	40.2252	(JASK)	10710		1	65.24.2	
1947	0.3035	IO INU	1	17.7201	0.2107	8MN	K/DN	1.34%	91 CPS	42歲2年
SA 7. 19 A-3	11.4968	[0.0567	1	18-1455	(14,176)	18457			44.01%	
A 18 26 A 1	0.4irm	10.1208	1	38.4853	0.438)	9,00	***************************************	1	44,49	
SA 50 26 4 2	0.5003	10 1121	=	16.7140	0.44(0)	185	SOCIA	5711	41 (6)%	93.78%
A 10 26 A 3	0.4850	10.092		37,6941	0.4325	19925		['LL 72'S	

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Day 0 Preparation Cons. (SA MA Analyzed on 11/29/2016, SA FE Analyzed on 11/16/2016)

Sample (II)	Sample Wt. (g)	Eysin Reagent Wil. (g)	Dave Level (ppm)	Penk Arm	Cale, Cont. (mg/ml.)	Date Cuae. (ppm)	Average (ppm)	%HS0	% Target	% Turget Average
SAMBAR	10,9090	13/1126#		344315	8.372h	10996	et sales e e	25 6 4 7	8/3 X/2%	dina jem digitaliyay
SAROAS	0.5000	45.1160		348943	0.1777	1295	11306	3.05%	A\$4132%	#5 A196
5A 0 6 8 7	0.518	15/017		159928	0,090	1119		3400	86.44%	
54 1 11 4 1	0.500	151037		103170	0.1951	11887	(AAAAAAAAAAAAAAAA	Etware/2007/A	90,524	***************************************
SA 4 11 A-2	0.50,9	1748/94		AKOU	0.4912	[214]	13697	1.58%	¥2.553.	42.27%
SA 4 11 A 3	0.5181	15,1270		34.8974	0.4290	12267			93,48%	
447 (DA I	0.5012	14.1641	1,1138	16.7512	0,1071	12032	***************************************		91,723	
SA 7 20 A-2	0.5129	13 2045		39.1280	0,4225	12534	12423	2819	45.47%	404,7074
54 1 20 A 3	0.5024	15 1561		1011105	16,1239	12712]	40,013	
A 19 27 A 1	0.5102	15.1569		276042	0.4062	1,20%43			จรถเร	
A 18 27 A 2	0.4016	15 1416		42,4,40	(1,4390)	12825	12923	7.05%	105,473	87***A
A 19-17A3	0.5033	15/1237		38,7567	0.4185	12581		1	\$45,909	
\$4.0 TA-t	0.5155	150(4	·····	36,3200	0.4153	12094			£10.75	
5A II TA-2	17,495h	15/0274		38,31,50	9,4,374	13564	130000	1 IMS	93.843	WIN74
5A II 7A I	0.5365	150927		19 4435	0.45%	(1960)			92,419	
A 1 11 A 1	0.5194	150001		-RIJ1184	0.4561	1,1251	***************************************		43.JH3	
54 4 14 A.2	0.5122	15.0737		40 B) 08	0.4559	1,415	13191	1.584%	9492%	93.339
M 1 14 A 3	15, 1435	(5 (42)		50,700	9.4205	12400			थ्ये गान	
A 7 - 21 A 1	0.5144	15.1119	14135	40.2469	6,4,924	13-467			4,6204	
A 7 ZI A Z	D.SIRM	15 (01)		37 13-110	84297	12780	13517	5.04%	41173	95 85%
A 2: 21 A A	0.4928	Sib-in		41,3554	s 4707	143391			1131 8.15	
A 10 28 A L	12,4114	[5][941		30,7745 0,4642	0.4642	13916			38.77	
A 10 28 A 2	0.4980	15 (46)		41.4408	9.4735	(43 IB	1,1262	1.393	301,114	U7, 56%
A In 28 A 3	0.5003	15 (9)51		17.8941	9.4326	1,050			572.3675	•

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 III	Nample Ws. (g)	Lynks Reagent Wil. (g)	Dose Level (ppm)	Prok Ares	Calc. Conc. (mg/ml.)	Dase Cane. (ppm)	Average (ppm)	%RSD	% Target	% Target Average
alvert m	334 (117)			******					S 3/15 S	
	\$20 Aug 166								27 (12 22	
	200	ASSAULT: STABBOK		\$0.44 A	A 400 - 100 A	SS001			W	
SA 4 11 A L	0.5166	(0.003)		37 2285	0.4103	(90,1)		I	પા કૃતિ	
84 4 H A-2	0.5124	104027		39,9241	0.4402	8645	828	4.344	VH 549	98 19%
5A + 11 A 3	0.5183	नं क्लेस्ट	97746	.08 0.522	0,4196	9295		1	92,56%	
47 BAT	13.5000	10.05%	75 140	374947	()-(()-()	180n T			92.245	
5A 7 18 A-2	0.4H3	103681		01.1901	0.3227	842%	8200	2415	90.10%	93,769
SAR BAS	0.5[19]	(M())(01		37.1Vt×	0.4135	HSIM		1	V2.6#3	
SA 10 25 A 1	0.5229	9,9113		11 H.M.S	93.4611	879.1			100.549	
A 10 23 A 2	0.4884	4.000		17. 4012	0.4129	HILL	8453	Time	97.543	W. D.V.
4 10- 25 4-3	().40%	10.050?		38.1735	0.4270	H4h.l		1	96,774	
SA 0. 6 A 1	0,4192	15 (I2nA		37.0226	(1, 4194 4	12031	***************************************	1	91.875	
5A 1 6 A-7	0.5000	15 (160	ESTER	47 7147	6,41W	12424	12063	1 4724	41.114	43.40%
SA 0-6 A.J	0,5181	15 1017		38.3277	0.4226	12:19		1	93,91%	
				3.5	4) ((25) -(([4,5)	*******************	***************************************	***************************************		

Colla shaded in that, gray were re-analyzed on 12005/2016 due to high % RSD.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 7 (Analyzed on 10/27/2016)

Sample ID	Semple Wr. (g)	Lysin Reagent Wt. (g)	Dose Ecrei (ppm)	Penk Arek	(mth/k) Centr Centr	One. (ppn)	(ppm)	%RSD	% Target	% larget Average
EX 1 V-1	1).3(f/n	533997	11	Nti	NA	NA	T		NA.	
£12.64	11.5366	50722	0 1	NO	NA.	NA	NA NA	NA	NA.	NA
CVIAG	0.559	3,0779	1 1	NU	I SA	¥A.	1		NA	
UNIC A-1	11.002	50)44		33,3544	(th.135	Olivir.	T		49,945	
CY 2 A-2	II.SUDH	5,0774	6093	77,9903	24000	6177	11.594	1.36/4	101 3738	[0] 06%
CY 2 A/3	0.5105	5,083	1 . 1	60,34%	06170	6211	1		192,355	
CYTAG	11.5299	101778		27.6531	0.2638	5,775			92639	
CV3A-2	11.5052	101522	44.14	25 MAN	0.25038	522.1	3120	1843	89.51%	VI 45%
1.9.3.4-3	0.503	10.0550	II	26 24-03	0.2667	5371	1		92.23%	
CYAA-I	0.3027	50330		195,3000	1.1505	11.00		11.75.17.7	11884	
CKANG	12.5048	5005	12118	(4.608)	1,0028	10019	ices	720%	81.34%	201775
CV4A-J.	E-2101	5,0570	98.5	14347-40405	Lion	11000		13 Ya	原見の映	
W.S.A.L	11.32.57	10004	Carriovi:	\$1249	0.59%	40001	4.00	1.00	WI SHA	Same and S
CV3 A-2	JL5197	10109000	41864	50,2725	0.32h7	ibise	(0076	34000	17.119	後性 排除
CV3A-J	II 5029	10.01602 ···	1. 1. 1. 20	47.7505	0.4936	9931	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	200 ST	MS3135	date vincent
CVAAL	0.50	130705	300 30	\$1,7243	0.500	17055	1.5000000	10,040,074	72,859	1 1 to 32 1 1
CYAA-2	8.5215	14.7364	18163	51.9749	0.51-03	1517	16208	525%	H3.71%	98.76%
CVAVA	17.5344	13.0972	100	35,11 18	0.300	SOME		interface with	HOUGH.	
CYAM	0.5134	150098	A service.	16.0137	0,4016	14107	ownsA	3.5	80.81%	French in 1800
CYTAZ	0.5273	15 1902	17757	44.2578	0.2621	13313	13655	1,48%	75.70%	7773%
EXTAG	11.5016	15.1000	45	42.6034	0.4450	13257	111 11 11 11 11 11	15 (15 mg)	WHOM.	

ND = Not Detected, NA = Not applicable.

Cells shaded in gray were resunalyzed on 10/31/2016 due to kiw signal.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Day 21 (Analyzed on 10/27/2816)

Sample II)	Numple We(g)	Lysis Reagent W.C.(g)	Dose Level (ppm)	Peak Area	Calc Cont (mp/p)	Dose Canc. (ppm)	Average (ppm)	%R\$0	% Farget	% Target Average
CVIAL	11337	रक्ष	1	NII	VA	NA.			N,s	
13.144	11.5(0.7	50770	1 0 1	80	NA NA	NA.	NA.	N.s.	BA .	NA.
CV 13-3	11.1219	3020	1 1	ND	NA.	NA	7		NA.	
CVPA-I	D. Shin	F13555	· · · · · · · · · · · · · · · · · · ·			-			יאליטיי	
L.F. 5.4.7	0.5121	50061	7007	(e) 1973h	3.702	6487	04600	3553	(4.117)	61.714
CV 4 A. 1	0.5022	513724	1 1	61.148	{in 504	est 20	1	1	172.1674	
CY 10 A-1	0.5272	512594		357407	0.5843	582	1		94.219	
CV 10 A-2	11 429	5.0610	54925 52 7617	52 7617	11,7554	4410	4,544	2003	Monot	01.80%
CV 10 A-1	IL.SIHA	5.0192	1 1	\$1.498V	4.561.1	594	1		IN STA	
CYITAI	11.51967	10,0415		35.4971	0.5025	11282		80 to 20 to	Anni Co	\$ 34(4/2) \$
UV 11 A-2	11.515(2.1	10.027X	100	30.2739	0.5999	J0905	1,0000	271%	25.178 871.425	79.15%
CVILAG	0.3615	laukes:	M. 18.1	\$3.0287	0.5563	11135	1 -45 - 4	400.00	75.76%	
CVIDAL	0.5120	10.035		\$1,5607	(1,1456	M621	1.07 (200) 1		8234%	a well of a
CV 12 A-2	D.986	10.1000	12001	#8.678W	0,506	19120	10548	1.799	28.400	\$1.76%
CV 12 A-2	11_9(143	10.0721	1968 500	3211438	0.5157	10000		Spring the	R1.49%	e in special and
CVIJAJ	0.3023	15.1293	3 : 25 : 25 : 3	70.1500	00221	1800		11.00	10.734	A CASE OF THE PARTY
CV DA-2	JT. Q146	15.1344	21043	57 11058	ONCHO	37025	Inva	4/64	PLUIS.	#1.53%
CVDAJ	0.50673	15.1557	100	54 8286	0.5736	12129	네 시간 100m/2	1.596.339	3516%	\$ 5 S. F. 60
CV MA-L	0.513	15.2176		47346	0.4954	34 03 \$	Daniel Co	3.50, 75.4	75.01%	a interest to
CV 14 A-2	0.5741	153631	14291	क्षेत्रप्रत	0.5118	15094		2979	78,31%	79.27%
EV 14 A-3	0.30	15000	al Section	49.60(6)	0.5218	15:516	1 4 A	14 × 28 ×	(III) 1984	Marini

ND - Not Detected, NA - Not applicable.

Cells shaded in gray were re-uralyzed on 10/31/2016 due to low signal.

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^{*} Excluded due to non-trending result

TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Days 7 and 21 (Analyzed on 19/31/2016)

Sample 1D	Sample WL (g)	Lyds Reugent Wt. (g)	Dose Level (ppm)	Penk Ares	Calc. Conc. (mg/g)	Ones Cests. (ppm)	Average (ppm)	%RSh	% Target	% Targe Average
EV 4 A-F	11,5027	30300		130,7878	11325	11342			112,377	·
154A-2	0.5048	50415	12118	1157.933	i Zeit!	12672] [3]89	57443	1102.87%	98.96¥
CVIA	0.3101	4 (0.404)	1 [118.7180	1.2617	12311	1		101.38%	
18544	0.5251	(1) 11494		40,1420	06219	144°t !			102.05%	
CV 5 A-Z	U_\$ 97	(0))(9)(11004	35 5551	0.994	1120	13-08	3,904	96.73%	יד וַאָּלָים
CVSAG	0.4074	((1))362	1 1	32 MHU	0.550)	11((1)	1		U4 15.95	
CY 6A-1	11.560	154733		(31.62.60	าเกลา	20000	1		109,363	
(YOA2	8.5233	19,7264	16(6)	01.5015	316500	HON	(UAKE)	\$ 21%	100 (11)%	(एस अध्य
1.764-1	12.544	1519072	1 i	06.44.36	0.200	14.14.5	7	1 1	107.759	
CVTAIL	R3114	13 0958	1	37.3489	016019	17857			97.274	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
(¥?A/2	B.\$273	15.[501	12767	35,340	0.5312	इंग्लिब	17238	1205	ul 184	91595
CVTAG	0.5016	15.1680	1 1	31 9133	0.5000	17116	1	! :	.93.21%	
CVIIA	0.5167	HOTHER	100	143,8008	0.5-20	13000	1 118.00	1000	FIF.88	200
CVILAG	0.5187	10.0272	14727	n3.5195	1893	12726	i i just	1.183	Maritime.	89.01%
CVIIAS	0.3015	100399	1000	64.1103	0.6733	13545	i i kanan	14. AZ	91.979	
CN 12 A-1	0.5128	1037707		67.11154	0.8655	1.5038	1		111 (1843)	
CV (2A-2	11,506	J41 (GF)O	12001	98,2956	0.6128	12171	12632	1414	9434%	UP Thris
CV 12 6.3	11,5043	(0)1722	1 1	1000011	06/21	39.25	1		1738/4	
CVBAL	11.5023	15,1995	1	n7 1985	(CAMS	21423	1		97618	
CV 13 A-2	II, YUA	15.1344	21941	(C) H189	(169%)	309)4	20090	3.193	94915	પ્યા. ગજ
CVHAS	11,4193	15 1557	1	64.2718	416/365	201111	[91,74%	
CV 14 A 1	11.515	15.2136	1	59.1638	(intal	18784	T		15374	
CYBAR	[[514]	15.(63)	19251	10.5%	0.613.0	187,00	18929	2003	177 (1/2)	97.6%
CV 14 A-3	11,507	(4)8(1)	1 [n1 K215	(IPGI)	19.173	1		11034745	

Cells shaded in gray were re-unalyzed on 12/05/2016 due to low signal.

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TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES

Study Days 0, 7 and 24 (Analyzed on 12/05/2016)

Sample ID	Sumple W.L. (g)	Lysis Reagent We (g)	Dose Level Lepmi	Peak Ares	('elt- Conc (mp/p)	Dree Conc. (ppm)	Average (ppm)	%RSD	% furget	% Target Average
CVIIAI	BA352	1082.5	**********	69.2555	0.7601	14474		***************************************	47,814	
CV II A-2	(2.523))	100164	14727	06.2234	ก 7245	1,000	14292	2615	44.23%	67.03°x
CVITAG	0.4191	103179	1 J	69.1265	11.7,114	14.987	1		99,170	
H04 A B-1:	0.995	\$1007	1877	47,7784	(15180	5317	517.3		110.00%	
1104AB2	U.5161.	5,1545	4373	42.1605	0,4508	1002	1873	6.97%	115.24%	131439
HUAN BA	1012.11	3.160	7 3			4760			169 06%	130
CY 9A-U	11.5114	\$1682	5	fights31	36657	186Z	27 347 3		92619	1 5 17 1
CVANA	11,5004	(84 5.1490		673114	0,7365	3,924	7.121	7054	301.31%	HOLL 1996
CVPAJ	0.506N	5.1544		70 9612	0.7769	THOR		81.031	105.639	
180 H2 A B-3	11,5231	\$51313.500		1(196)	49,11484	en zu			44.66/3	
HO 10 A B 7	11.415	HURST	8746	SS STREET	0.4040	7002	402 TH	44005	01374	54,134.
HO ID A B-1	8,484	il 'Albert	1 1	57 HS52	(1,11,6)	8131	1		112 1177	
HO HATEL	0.5139	15,1945		38 4 No. 1	राबशाह	12419			6475	
HOHATE	0.5051	15.1-646	10118	(8:345)	ONSHA	12951	12226	1.70%	057,93	93,2104
HO MAT 3	11,985	15.2688	1 1	354051	0.3395	11697	1	!	89.179	
SAD 2A-1	0.5212	51675	·····	£2.4467	0.4047	1573			IDAGES.	
54 D 2 A 2	0.5251	5.1MVC	4373	4) 4(3)	fi.ANK	4725	450N	5004	1100 (15%	रात्र होता
SAD 2A3	11,5184	3,(5) [1 1	35.319	0.4233	43%	1]	96.189	
5A 10- 27 A-L	U.5325	£52209	202 7	98.72(R	0.4011	31431	180((4.1)	7,617, 644	47.453	24.15
SA ID. 27 A.2	0.3017	152743	CHIRA	31-8336	ELV-78	inité	10591	7.49%	77.14%	- 200 APW
SA 10 ZT A-1	11.3304	£52(1)	10000	72.500R	(13.57	317,056	1	1.38/5.1	70,015	A TECRET
5A9 4A1	0.5243	12.55.0		38 (1974	0.4162	7938	1		90.51%	
SA 0 4A-2	11.5322	100217	87.46	35,9961	0.4230	MEC	7951	0.57%	91.303	90,91%
540 443	11,50.51	13102034	1	N 59738	0.45%	74.11	1		F260.130	40,914

Cells shaded in grap, were excluded from analysis due to high SiRSD. Original data was used in analysis.

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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-43-1d- (b)
PSL No. 1-0720-5R

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)

Kristina R. Vygantas, DVM Diplomate, American College of Veterinary Ophthalmologists

APPENDIX F: INDIVIDUAL ANIMAL IN-LIFE CLINICAL OBSERVATIONS1

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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.

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	В	9	1 0	1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9
1	m	7001	No Abnormalities Detected		Х	Х	Χ	Х	Х	Χ	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х
		7002	No Abnormalities Detected		Х	Х	Χ	Х	Х	Х	Χ	Х	Х	Х	Х	X	X	Χ	Х	Х	Х	Х	Χ	X
		7003	No Abnormalities Detected		X	Х	Χ	Х	Х	Х	Χ	Х	Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Х	Χ	Х	Х
		7004	No Abnormalities Detected		X	Х	Х	Х	Х	Х	Χ	Χ	Χ	Х	Х	Χ	X	Х	X	X	X	Х	Х	Х
		7005	No Abnormalities Detected		Х	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	Χ	Х	Х	Х	X	Χ	Χ	Х	Х	Х
		7006	No Abnormalities Detected		Х	Х	Χ	Х	Χ	Χ	X	Х	Х	Χ	Х	Х	Х	Х	Χ	X	Χ	Χ	Х	Х
		7007	No Abnormalities Detected		X	Х	Χ	Х	Х	Χ	Χ	Χ	Χ	Х	Х	Х	X	Х	Х	Χ	Х	Χ	Х	Х
		7008	No Abnormalities Detected		Х	Х	Χ	Χ	Х	Χ	X	Х	Х	Х	Х	Х	Х	Х	Χ	Χ	Χ	Х	Х	Χ
		7009	No Abnormalities Detected		Х	Х	Х	Х	Χ	Χ	X	Χ	Х	Х	Х	Х	Χ	Х	Χ	Х	Χ	Χ	Х	Х
		7010	No Abnormalities Detected		х	Х	Χ	Χ	χ	Х	Х	Х	Х	Х	Χ	Χ	X	Χ	Χ	Х	Х	Х	Х	Х

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

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Day numbers relative to Start Date

					2	2	2	2	2	2	2	2	2	2	3
Grou	up Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	0
1	m	7001	No Abnormalities Detected		Х	Х	Х	х	Х	Х	X	Х	Х	X	
		7002	No Abnormalities Detected		Х	Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	
		7003	No Abnormalities Detected		X,	Х	Х	Χ	Х	Χ	Χ	Χ	Х	Χ	
		7004	No Abnormalities Detected		Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Х	Х	
		7005	No Abnormalities Detected		Х	Х	Χ	Χ	X	X	Χ	Х	Х	Х	
		7006	No Abnormalities Detected		Х	Х	Χ	Χ	Χ	X	Х	Х	X	Х	
		7007	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Х	Χ	
		7008	No Abnormalities Detected		X	Х	Х	Χ	Х	Χ	Χ	Х	Х	Х	
		7009	No Abnormalities Detected		Х	Χ	Χ	Χ	Х	Х	Χ	Х	Х	Х	
		7010	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	

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Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Grou	p Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	1 0	1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9
2	m	7021	No Abnormalities Detected		Χ	Х	χ	Х	Х	Х	Х	Х	Χ	χ	Χ	χ	Х	Х	Х	Х	Х	Х	х	Х
		7022	No Abnormalities Detected		Х	Х	Χ	X	Χ	Х	Χ	Х	Х	Х	Χ	Χ	Χ	Χ	X	X	X	Χ	X	X
		7023	No Abnormalities Detected		Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	X	Х	Х
		7024	No Abnormalities Detected		Х	Χ	X	X	Х	Χ	Х	Χ	Х	Χ	Х	X	X	Χ	X	Χ	X	X	Х	Χ
		7025	No Abnormalities Detected		X	Х	Χ	Χ	X	X	Χ	Χ	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Х	Х	X
		7026	No Abnormalities Detected		Х	Х	Χ	Χ	X	X	Х	Χ	Χ	Х	Х	Χ	Χ	Χ	Х	X	Χ	Х	Х	Χ
		7027	No Abnormalities Detected		X	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	X	Χ	X	Х	Χ	Х	Х
		7028	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	X	Χ	Х	Х	Х	X	Χ	Χ	Χ	Χ	Χ	Х	Х	Χ
		7029	No Abnormalities Detected		Х	Х	Х	Χ	X	X	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х
		7030	No Abnormalities Detected		Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	X	Х	X	Х	Х	Х	X	X

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Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

					2	2	2	2	2	2	2	2	2	2	3
Gro	up Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	0
2		7021	No Abnormalities Detected			х									
2	m	,			۸	^		Α.	Х	Х	Х		X	Х	•
		7022	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	χ	Х	Х	Х	
		7023	No Abnormalities Detected		Х	X.	Χ	Х	Χ	X	X	Χ	Χ	Х	
		7024	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Х	
		7025	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Х	Х	Χ	Χ	
		7026	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	Χ	Х	Х	Х	
		7027	No Abnormalities Detected		Х	Х	Х	X	Χ	X	Х	Х	Х	Х	
		7028	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	
		7029	No Abnormalities Detected		Х	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	
		7030	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

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	1 0	1	1 2	1 3	1	1 5	1 6	1 7	1 8	1 9
3	m	7041	No Abnormalities Detected		Х	X	X	X	Χ	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х
		7042	No Abnormalities Detected		X	Х	Х	X	X	X	Χ	Х	Х	Χ	Х	Х	X	X	Х	Х	Х	Х	Х	Χ
		7043	No Abnormalities Detected		Х	Χ	Χ	X	X	Χ	Х	Х	Х	Х	Х	Х	Χ	Χ	Х	Х	Х	Х	Х	Χ
		7044	No Abnormalities Detected		Х	Х	Χ	X	X	Х	Х	Х	Х	Х	Х	Χ	Χ	Χ	Х	Х	Х	Х	Х	Χ
		7045	No Abnormalities Detected		Х	Χ	Χ	Χ	Х	X	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х
		7046	No Abnormalities Detected		Х	Х	Χ	Х	Х	Χ	Χ	Χ	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Χ
		7047	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	Χ	Х	Χ	Х	Х	Х	Χ	Χ	Χ	Х	Х	Х	Х	Х
		7048	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	Х	Χ	Х	Х	Х	Х	X	Х	Х	Х	Х	Х	Х	Χ
		7049	No Abnormalities Detected		Х	Х	Х	Х	Х	X	Χ	Х	Х	Χ	Х	Χ	Χ	Χ	Χ	Х	Χ	Χ	Χ	Х
		7050	No Abnormalities Detected		Х	Х	Χ	Х	Х	Х	Χ	Χ	Х	Х	Х	Х	Χ	Х	Χ	х	Х	Χ	Χ	Х

M = Moderate; F = Superficial

Severity Codes: X = Present; S = Slight;

PSL Study Number 43166 A 28-Day Dietary Study in Rats

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Day numbers relative to Start Date

					2	2	2	2	2	2	2	2	2	2	3
Grou	лр Ѕех	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	0
3	m	7041	No Abnormalities Detected		Х	Х	X	Х	Х	Х	х	Х	Х	Х	
		7042	No Abnormalities Detected		Х	Χ	Χ	Х	Χ	Χ	Χ	Χ	Х	Х	
		7043	No Abnormalities Detected		Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Х	
		7044	No Abnormalities Detected		Х	Χ	Х	X	Х	Χ	X	Χ	Χ	Х	
		7045	No Abnormalities Detected		Х	Χ	Х	Χ	Χ	Χ	Χ	X	Χ	Х	
		7046	No Abnormalities Detected		Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	
		7047	No Abnormalities Detected		Х	Х	Χ	Χ	Χ	Χ	X	Χ	X	X	
		7048	No Abnormalities Detected		Х	Х	Χ	X	Х	Х	X	Х	Х	Х	
		7049	No Abnormalities Detected		Х	Χ	Χ	Χ	Χ	Χ	Χ	X	Χ	Х	
		7050	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	

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Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

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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	1 0	1 1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9
4	m	7061	No Abnormalities Detected		Х	Х	X	Х	Х	Х	Х	X	Х	х	X	Х	Х		Х	х	X	х	х	x
			Staining	Cage Pan														Х						
		7062	No Abnormalities Detected	-	Х	Х	Х	Х	Х	Х	Χ	Χ	Х	Х	Х	Х	Χ	Χ	Х	X	X	Х	Х	Х
		7063	No Abnormalities Detected		Х	Х	Х	Х	Χ	X	Χ	Χ	Х	Χ	Х	Х	Χ	Χ	Χ	Х	χ	Х	Х	Х
		7064	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Χ	Χ	Χ	X	Х	Х	X	Х	Χ	Χ	Х	Χ	Х	Х
		7065	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Χ	Х	Х	Х	Х	Х	Х		Х	Х	Х	Х	Х	Х
			Staining	Cage Pan														Х						
		7066	No Abnormalities Detected		X	Х	Х	Х	Χ	Х	Χ	Χ	X	Х	Х	Χ	Χ		X	Х	Х	Х	Х	Х
			Staining	Cage Pan														Χ						
		7067	No Abnormalities Detected		Х	Х	Χ	Х	Х	Χ	X	X	Х	X	Χ	Χ	X		X	Χ	Х	Χ	Х	Χ
			Staining	Cage Pan														Х						
		7068	No Abnormalities Detected		Х	Χ	Х	X	X	Χ	X	Χ	Χ	Χ	Х	Χ	Х		Х	Χ	Χ	Х	Х	Х
			Staining	Cage Pan														Х						
		7069	No Abnormalities Detected		Х	Х	Х	Χ	Х	X	X	Χ	Х	X	Х	X	Χ		X	X	Χ	X	Х	Х
			Staining	Cage Pan														Χ						
			Eschar	Head																				
		7070	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	X	χ	Х	Х	Х	Х	Х		Х	Χ	Х	Х	Х	Х
			Staining	Cage Pan														Х						

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Severity Codes: X = Present; S = Slight; M = Moderat

M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Grou	p Sex	Animal	Clinical Sign	Site	2 0	2 1	2 2	2 3	2 4	2 5	2 6	2 7	2 8	2 9	3 0
4	m	7061	No Abnormalities Detected		Х	X	×	х	х	X	X	X	х	X	
			Staining	Cage Pan											
		7062	No Abnormalities Detected		Х	Χ	Χ	Χ	Χ	χ	Χ	Χ	X	Х	
		7063	No Abnormalities Detected		Х	Χ	Χ	Х	Χ	X	X	Χ	Χ	Х	
		7064	No Abnormalities Detected		Х	Х	Χ	Х	X	Х	Χ	Χ	Х	Х	
		7065	No Abnormalities Detected		Х	Χ	Χ	Х	X	Х	Χ	Χ	Χ	Х	
			Staining	Cage Pan											
		7066	No Abnormalities Detected	_	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	
			Staining	Cage Pan											
		7067	No Abnormalities Detected	_	Х	Χ	Х	Х	X	X	Х	Х	Х	Х	
			Staining	Cage Pan											
		7068	No Abnormalities Detected	_	X	Χ	X	Х	Х	Χ	Χ	Χ	Х	Х	
			Staining	Cage Pan											
		7069	No Abnormalities Detected	_	Х	Χ	Χ	Х	X	Х	Χ	Х			
			Staining	Cage Pan											
			Eschar	Head									F	F	
		7070	No Abnormalities Detected		Х	Х	Х	Χ	Χ	X	Χ	Х	Х	Х	
			Staining	Cage Pan											

M = Moderate; F = Superficial

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PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

Grou	p Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	1 0	1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9
1	f	7011	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Χ	X	Х	Χ	х	Х
		7012	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Х	Х	Х	X	Х	Х	Х	Х	Χ	Х	Х	Χ	X	X
		7013	No Abnormalities Detected		Х	Χ	Χ	Х	Χ	Χ	Χ	Χ	Χ	Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Х	Х	Χ
		7014	No Abnormalities Detected		Х	Χ	Χ	X	Χ	Х	Χ	Χ	Х	Х	Χ	Х	Χ	X	X	Х	Χ	Χ	X	Х
		7015	No Abnormalities Detected		х	Χ	Χ	Χ	Х	Χ	Χ	Х	Х	Х	Х	Х	Χ	X	Χ	Х	Χ	Х	Х	X
		7016	No Abnormalities Detected		Х	Х	Х	Х	Χ	X	Х	X	Χ	Х	Χ	Х	Х	Χ	Χ	Χ	X	Х	Х	Х
		7017	No Abnormalities Detected		Х	Χ	Х	X	Χ	Χ	X	Χ	Х	Х	Х	Х	X	Χ	Χ	Х	Χ	Х	Х	Х
		7018	No Abnormalities Detected		Х	Х	Х	Х	X	Χ	Х	Х	Х	Х	Х	X	Х	Х	Χ	Χ	Х	Х	Х	Х
		7019	No Abnormalities Detected		х	Х	Х	Х	Χ	X	X	Χ	Х	Χ	Χ	Χ	Χ	X	Х	Χ	Х	Х	Х	Х
		7020	No Abnormalities Detected		х	Х	Χ	Χ	Χ	Χ	Χ	Х	Х	Χ	Х	Х	Х	Х	Χ	Х	Χ	Χ	Х	Х

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

							2	2	2	2	2	2	2	2	2	2	3	
Group Se	X	Animal		Clinical S	ign	Site	0	1	2	3	4	5	6	7	8	9	0	
1 f		701 1	No	Abnormalities	Detected		Х	X	х	Х	Х	Х	Х	X	Х	X	Х	
		7012	No	Abnormalities	Detected		Х	Χ	Χ	Х	Χ	χ	Χ	Χ	Χ	Χ	Х	
		7013	No	Abnormalities	Detected		Х	Χ	Χ	Χ	Χ	Χ	X	Χ	Χ	Х	Х	
		7014	No	Abnormalities	Detected		Х	Х	Х	Х	Χ	X	X	Х	Х	Χ	Х	
		7015	No	Abnormalities	Detected		X	Х	Χ	Х	Χ	Χ	Х	Χ	Χ	Х	Х	
		7016	No	Abnormalities	Detected		Х	Χ	Χ	Х	Х	Χ	Χ	Х	Х	Х	Х	
		7017	No	Abnormalities	Detected		X	Χ	Χ	Х	X	Χ	Х	Х	Х	Χ	X	
		7018	No	Abnormalities	Detected		Х	Х	Х	X	Х	Χ	Χ	Х	Х	Х	Х	
		7019	No	Abnormalities	Detected		Х	Χ	Χ	Х	Χ	Χ	Χ	Х	Х	Х	Х	
		7020	No	Abnormalities	Detected		Х	Χ	Χ	Х	Χ	Χ	X	Х	Χ	Χ	X	

F = Superficial

Severity Codes: X = Present; S = Slight; M = Moderate;

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	0	1	2	1 3	4	1 5	1 6	1 7	1 8	9
2	f	7031	No Abnormalities Detected		Х	Х	Х	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	χ	Х
		7032	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Х	Х	Χ	Х	Х	X	Х	Х	Χ	Χ	X	Х	Х	Χ
		7033	No Abnormalities Detected		X	Х	Х	Χ	Χ	Х	Χ	Χ	Х	Χ	Х	Х	Х	X	Х	X	X	Х	Χ	Χ
		7034	No Abnormalities Detected		Χ	X	Х	Х	Х	Χ	Χ	Χ	Х	Χ	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Х
		7035	No Abnormalities Detected		Х	Х	Х	Х	Χ	Х	X	X	X	Х	X	Х	Х	Х	Χ	Χ	Χ	Х	Х	Χ
			Alopecia	Left Forelimb																				
			Alopecia	Right Forelimb																				•
		7036	No Abnormalities Detected		Х	Х	Х	Х	Χ	Х	X	Χ	Х	Χ	Х	Х	Х	Χ	Χ	Χ	Х	Х	Х	Х
		7037	No Abnormalities Detected		Χ	Х	Х	Χ	X	Χ	X	Х	X	Χ	Х	Х	Х	Х	Х	Χ	X	Х	Χ	Х
		7038	No Abnormalities Detected		Χ	Х	Χ	Х	Χ	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Χ	X	Χ	Χ	Х	Χ
		7039	No Abnormalities Detected		Χ	Χ	Х	Χ	Х	Χ	Χ	Χ	Χ	Х	Χ	Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	Х
		7040	No Abnormalities Detected		Χ	Х	Х	Х	Х	Χ	Χ	Χ	Х	Х	Х	Х	Χ	Χ	X	X	Χ	X	X	Х

Severity Codes: X = Present; S = Slight; N

M = Moderate; F = Superficial

PSL Study Number 43166 A 28-Day Dietary Study in Rats

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Day numbers relative to Start Date

					2	2	2	2	2	2	2	2	2	2	3
Group	o Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	0
2	f	7031	No Abnormalities Detected		Х	Х	X	X	X	X	X	X	Х	Х	X
		7032	No Abnormalities Detected		Х	Х	Х	Х	Х	X	Χ	X	Х	Х	Х
		7033	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Χ	Х	Χ	Χ	Х
		7034	No Abnormalities Detected		Х	X	Х	Χ	Χ	Χ	Χ	X	Х	Х	Х
		7035	No Abnormalities Detected		Х										
			Alopecia	Left Forelimb		S	S	S	S	s	s	S	М	М	М
			Alopecia	Right Forelimb		S	S	S	S	S	s	S	М	М	М
		7036	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	Х	X	Χ	Х	X
		7037	No Abnormalities Detected		Х	Х	Х	Х	Х	Χ	X	X	Χ	Х	Х
		7038	No Abnormalities Detected		Χ	Χ	Х	Х	Х	Х	Χ	Х	Χ	X	Х
		7039	No Abnormalities Detected		Χ	Х	Х	X	X	X	X	X	Χ	Χ	X
		7040	No Abnormalities Detected		X	Х	Х	Х	Х	X	Х	X	Х	Х	X

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PSL Study Number 43166 A 28-Day Dietary Study in Rats

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Day numbers relative to Start Date

Grou	p Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	1 0	1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9
3	f	7051	No Abnormalities Detected		Х	Х	Х	Х	Χ	Χ	X	Χ	Х	Х	χ	Х	Х	Х	Х	Х	Х	Х	Х	X
		7052	No Abnormalities Detected		Х	Х	Χ	Х	Χ	Х	Χ	Χ	Х	Χ	Х	Χ	Χ	Χ	Χ	Χ	Х	Х	Х	Х
		7053	No Abnormalities Detected		Х	Х	Χ	Х	Χ	Χ	Х	Х	Х	Х	Х	Х	Χ	Χ	Χ	Χ	Χ	Х	Х	Х
		7054	No Abnormalities Detected		X	Х	Χ	Х	Χ	Χ	Χ	Х	Х	Χ	Χ	Х	Х	Χ	X	Х	Χ	Х	Х	Χ
		7055	No Abnormalities Detected		Χ	Х	Х	Χ	X	Х	Χ	Х	Х	Х	Χ	Χ	Х	Χ	Х	Х	Χ	Х	X	X
		7056	No Abnormalities Detected		Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Х	Х	Χ	Χ	Х	Χ	Χ	Χ	Х	X	Х	X
		7057	No Abnormalities Detected		Х	Х	Χ	Х	Х	Х	Х	Х	Χ	Х	Х	Χ	Χ	Χ	χ	Χ	Χ	Х	Х	Χ
		7058	No Abnormalities Detected		Х	Χ	X	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Χ	Χ	Χ	Χ	X	Χ	Х	Χ
		7059	No Abnormalities Detected		х	X	X	X	Х	Х	X	X	Х	Χ	Х	Х	Χ	Х	Χ	Х	Χ	Х	Х	Χ
		7060	No Abnormalities Detected		х	Х	Х	Х	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Χ	Х	Х	Χ

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PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

					2	2	2	2	2	2	2	2	2	2	3
Gro	up Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	0
3	 f	7051	No Abnormalities Detected		Х	X	X	X	X	X	X	Х	x	X	X
		7052	No Abnormalities Detected		Х	X	Χ	X	Χ	X	Х	Χ	Χ	Х	Х
		7053	No Abnormalities Detected		Χ	Χ	Х	Χ	Χ	Χ	Х	Χ	Χ	Х	Х
		7054	No Abnormalities Detected		Χ	Х	Х	Х	Х	X	Х	Χ	Х	Х	Х
		7055	No Abnormalities Detected		X	Χ	Χ	Χ	Χ	Χ	X	X	Х	Х	Х
		7056	No Abnormalities Detected		X	X	Χ	Х	Χ	Χ	Χ	X	Х	Х	Х
		7057	No Abnormalities Detected		Х	Χ	Χ	Χ	X	Χ	Х	Χ	X	Х	Х
		7058	No Abnormalities Detected		X	Х	Χ	Х	Х	X	Χ	X	Х	Х	X
		7059	No Abnormalities Detected		Х	Х	Х	Χ	Х	Χ	Х	Χ	Χ	Χ	Х
		7060	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х

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Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

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	0	1	2	3	4	5 	6	7	8	9
4	f	7071	No Abnormalities Detected		х	х	Х	Х	Х	Х	X	Х	Х	X	х	Х	Х	X	Х	х	Х	Х	Х	Х
		7072	No Abnormalities Detected		Х	Х	Х	Χ	X	Χ	X	Х	Χ	X	Х	Х	Χ	X	Х	Х	Х	Х	X	Х
		7073	No Abnormalities Detected		Х	Х	Х	Х	X	Χ	Χ	Χ	Х	Х	Χ	Х	Χ	Χ	X	Χ	Х	Х	Χ	Х
		7074	No Abnormalities Detected		Х	Х	Х	Χ	Χ	X	X	X	Х	Χ	Х	Х	Χ	Χ	Χ	Х	Х	Х	Х	Х
		7075	No Abnormalities Detected		X	Х	Х	Х	X	Χ	X	Х	Χ	Х	Х	Χ	Χ	X	X	X	Χ	Х	X	Х
		7076	No Abnormalities Detected		Х	X	Χ	Χ	Х	Χ	Χ	X	Χ	Х	Х	Х	Χ	Х	X	Х	Χ	Х	Х	Χ
		7077	No Abnormalities Detected		Х	Х	Х	Х	Χ	Χ	Χ	Х	Х	Х	Χ	Х	Х	Χ	Х	Χ	Χ	Χ	Х	Χ
		7078	No Abnormalities Detected		Х	Х	Х	Х	Χ	X	Χ	X	Χ	Х	Х	Х	Χ	Χ	Χ	Х	Χ	Χ	Х	Χ
		7079	No Abnormalities Detected		Х	Х	Х	Х	Χ	Χ	Χ	X	Х	Х	Х	Х	Χ	X	X	X	Χ	Χ	X	Х
		7080	No Abnormalities Detected		Х	Х	Х	Х	X	X	X	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х

Severity Codes: X = Present;

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Group 1 - 0 mg/kg/day Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Group 2 - 512 mg/kg/day

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					2	2	2	2	2	2	2	2	2	2	3
Grou	up Sex	Animal	Clinical Sign	Site	0	1	2	3	4	5	6	7	8	9	0
4	f	7071	No Abnormalities Detected		Х	х	Х	X	X	Х	Х	Х	X	Х	Х
		7072	No Abnormalities Detected		Χ	Χ	Х	X	X	Χ	Χ	Χ	Х	X	Х
		7073	No Abnormalities Detected		Х	Χ	X	Χ	Χ	X	X	X	Χ	X	Х
		7074	No Abnormalities Detected		Х	Χ	Х	Х	Χ	Χ	Χ	Х	Χ	Х	Х
		7075	No Abnormalities Detected		X	Χ	X	Χ	X	Χ	Χ	Х	Х	Х	Х
		7076	No Abnormalities Detected		Х	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Х	Х	Χ
		7077	No Abnormalities Detected		Х	Χ	X	Х	Χ	X	Х	Х	Χ	Х	X
		7078	No Abnormalities Detected		Х	Χ	Х	Χ	Χ	Х	Х	Х	Х	Х	X
		7079	No Abnormalities Detected		Х	Х	Χ	Х	Χ	Χ	Х	Х	Х	Х	Х
		7080	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	х	Х

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

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 an	d Open Field Observations
Activity/Arousal	 Alternating behaviors - animal goes through normal repertoire of behaviors during observation period. These consist of exploring, sniffing, grooming, rearing, etc. 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. Hypoactive/Not alert - animal sits in one place during the observation period. Animal appears to be unaware of its surroundings or in a stupor. 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	None Biting cage Self-mutilation
Circling	Absent Present
Convulsions	None Clonic – alternating periods of contraction and relaxation of muscles Tonic – prolonged period of muscle contractions
<u>Defecation</u>	None/Normal Soft (partially formed) Diarrhea (watery feces)
Ease of Removal/Handling	 Slight/moderate resistance - animal is easy to handle, may squirm or vocalize occasionally. No resistance - animal is limp/flaccid when being handled. High resistance/aggressive - animal is difficult to handle, and/or squirms continuously, and/or tries to bite handler. Aggressive - biting or lunging behavior specifically directed at handler.
Emaciation	O. Absent Present (confirmed using body weights)
Eyes	Normal Exophthalmos - abnormal protrusion of eyeball Endophthalmus - sunken eyeball Endophthalmus - sunken eyeball Eye damaged - mechanical damage (e.g. orbital bleeding, etc.)
Fur/Skin Appearance	O. Normal O. Unkempt - coat rough or ungroomed, may be slightly stained Urine stained/wetness (Ano-genital staining) Hair loss
Gait	Normal Normal limbs exaggerated/splayed, hind limbs and/or forelimbs show exaggerated placement or movement Non weight bearing (Limping)
<u>Lacrimation</u>	Absent Present - lacrimation noticeable. Excessive - animal has excessive amount of tearing. Note: Descriptors (i.e. color of ocular discharge will be noted on daily observation sheet).
Locomotion	Normal Somewhat impaired Totally impaired

APPENDIX G (cont.): DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

Mucous Membranes	Normal Present – mucous noticeable
	2. Excessive – animal has an excessive amount of mucous present
Muscle Tone	 Normal - muscles are resilient and firm and the hind legs go through their full range of motion. Increased - muscles are rigid, hind limbs will not go through their full range of motion. Decreased - muscles are flaccid, hind limbs have little or no resistance to movement
Palpebral Closure	O. Eyes wide open I. Eyes halfway shut Eyes completely shut
Piloerection	0. Absent 1. Present
<u>Posture</u>	O. 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	None Present - salivation is noticeable around the edge of the mouth Excessive - salivation extends to the fur around the jaw
Tremors	O. 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	Absent Present – Be specific in describing all unusual behaviors on data sheet.
<u>Urination</u>	0. None/Normal 1. Excessive
Vocalization, removal from cage	O. Absent 1. Present - animal vocalizes unprovoked or continuously vocalizes when being handled.
Vocalizations, open field observations	0. Absent 1. Present
Writhing	Absent Present
Manipulative Tests	
Pupillary reflex	Normal Slow or absent- pupil reaction is slow or absent.

APPENDIX H: INDIVIDUAL ANIMAL DETAILED CLINICAL OBSERVATIONS¹

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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

						Deg	Clin Obs (Ren	DetCliaObs (Removal from Cage)	2					
gkg/day roup 1	Handing Reactivity	Handling Reactivity	Handling Reactivity	Hwndling Reactivity	Handling Reaclivity	Handling Vocalization Vocalization (RC) (RC) (RC) (RC) (RC)	Vocalization (RC)	Voculization (RC)	Vocalization (RC)	Pocalization (RC)	Palpebral Closure	Paprebral Closure	Palpebral Closure	Papeeral Closure
	0	٠	7	21	38	٥		14	12	8;	0	7	14	21
1002	0	0	0	0	c	0	o	٥	0	0	0	0	0	0
7007	0	0	0	۰	٥	۰	٥	۰	٠	•	•	٠	Ð	0
2003	٥	0	0	¢	0	•	0	٥	•	0	-	•	φ	0
100	6	0	٥	٥	٥	۰	•	0	۰	0	•	0	0	0
2002	0	0	0	0	0	0	0	0	0	-	0	¢	0	c
7006	0	0	0	0	0	۰	0	0	0	•	0	0	0	0
2007	•	۰	0	0	٥	٥	0	0	9	•	o	0	0	Φ
2002	φ	۰	0	0	0	0	0	0	•	-	0	0	0	0
5002	•	۰	0	٥	0	•	٥	0	•	•	•	0	0	٥
7010	0	0	0	0	0	0	0	•	0	٥	•	0	0	0

Individual Animal Detailed Clinical Observations

PSL. Study Number 43166 A 28-Day Dietary Study in Rats

Sec: Male Day(s) Relative to Start Date

0						DetC	DetClinObs (Removal from Cage)	eval from Ca	ige)					
mgkg/day Group I	Palpebral Closure	Phipebral Lactination Lactination Lactination Lactination Lactination Closure	Lucrimation	Lacrimation	Lacrimation .	Lacrimulion	3 /G	ýg	Byc	E)c	ž(a	Membranes	Membranes Membranes Membranes	Mucous
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1002	0	0	0	Đ	0	0	٥	٥	٥	0	0	0	٥	0
7002	٥	٥		0	0	•	۰	0	•	0	٥	•	٥	0
7003	0	٥	0	•	0	0	•	•	0	0	٥	0	•	0
1001	۰	۰	0	0	0	•	•	0	0	٥	٥	0	0	0
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7006	0	٥	0	•	9	•	•	0	0	٥	0	•	٥	0
1007	0	۰	0	٥	٥	0	•	•	0	٥	0	٠	0	0
2002	0	0	0	0	0	0	•	•	0	٦	0	٥	0	0
4007	٥	0	۰	0	۰	0	•	۰	0	٥	0	۰	0	9
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Individual Animal Detailed Clinical Observations

						Del	DelClinObs (Removal from Cage)	oval from Ca	(38)					
mpkyday Group 1	Mucous Mucous Membranes Membranes	Membranes	Saivation	Salivation Sulivation	Sulivation	Salivation	Salivation Solivation	Emaciation	Emaciation Emaciation Emaciation Emaciation Emaciation Proceection	Emaciation	Emaciation	Emaciation	Piloerection	Piloerection
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7001	Þ	0	Ð	0	o	0	0	0	0	0	0	0	0	÷
7002	٩	>	0	٥	0	0	۵	•	•	•	0	5	9	3
7003	٥	0	٥	٥	0	0	0	0	•	•	٥	٥	0	•
7001	٥	0	0	0	٥	•	٥	•	0	0	0	•	0	0
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7007	٥	0	0	٥	٥	0	0	0	\$	0	0	9	Þ	٥
7008	•	0	0	•	0	٥	0	0	٠	5	0	\$	0	٥
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7010	¢	c	c	=	<	٠	4	_	=	=	٠	<		ء

Individual Animal Detailed Clinical Observations

The state of														
						Detc	DetClinObs (Removal from Cage)	oval from Ca	(3c)					
nigkęday Group I	Pilogection	Pilocretion	Plocection Pilocretion Pilocretion FurSkin		Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone,	Muscle Tonel	Muscle Tone	Purskin Niusete ToneMusete ToneMusete ToneMusete ToneMusete Tone Respiratory Pattern	Respiratory Pattern
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7003	٥	0	0	0	٥	0	•	0	0	0	٥	•	0	0
7004	0	•	o	c	٥	•	•	۰	0	0	•	•	0	0
7005	0	0	o	0	0	0	•	0	С	0	•	•	0	0
7006	•	•	•	0	•	•	•	0	0	•	0	•	•	÷
7007	٠	•	0	٥	0	•		0	0	•	۰		0	0
7008	٥	0	0	٥	0	Đ	0	0	-	0	•	-	0	Ð
4005	٥	۰	0	٥	0	۰	•	0	•	0	•	•	٥	Đ
7010	0	<u></u>	0	¢	0	0	0	c	•	0	•	_	c	-

Individual Animal Detailed Cánical Observations

PSL Study Num A 28-Day Dielary S

Sex: Male Day(s) Relative to Start Date

				DetClinOn	DetClinOhs (Removal from Cage)	rom Cage)					DetClino	DetClinObs (Open Field Obs)	eld Obs)	l
mg/kg/day Group i	Respiratory	Respiratory Respiratory Respiratory	Respiratory	12	Pupilitary	Pupillary	Pupiliary	Pupillary P. D.	Pupillary	Activity	Activity/	Activity/	Activity/	Activity/
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1001	0	0	0	0	٥	٥	0	0	0	٥	0	0	0	ľ
7002	۰	0	0	5	0	•	0	٥	0	•	>	0	0	7
7003	•	0	0	٥	0	0	0	0	0	•	0	0	0	9
7001	•	0	0	•	•	•	٥	0	0	•	•	0	0	•
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7006	٥	٥	0	0	0	0	0	0	0	•	0	۰	0	2
7007	٥	۰	٥	٥	•	0	0	0	o	•	0	٥	0	.
7038	٥	۰	0	٥	0	0	0	•	0	0	0	0	0	0
7005	٥	•	٥	0	0	0	•	0	0	۰	٥	0	0	3
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mpkyday Group 1	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions Convulsions Convulsions Convulsions Tranors		Tremors	Tranors	Tremon	Ткяпогу	Posture	Posture	Posture	Posture
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1007	o	0	0	0	0	0	0	0	o	٥	0	٥	0	٥
7002	٥	0	۰	•	0	0	0	۰	0	٥	۰	•	-	Þ
7003	٥	0	۰	0	0	0	0	۰	0	٥	0	٥	0	Ф
7001	٠	0	٥	0	0	0	0	•	Q	۰	۰	e	•	Ф
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7008	0	٥	•	\$	0	0	0	•	•	0	٥	0	0	0
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Individual Animal Detailed Clinical Observations

Sec. Male Day(s) Relative to Start Date

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			-	0 0	0	0 0	0	0	0	0	0 0	0	

Individual Animal Detailed Cinical Observations

						ď	DetClinOhs (Open Field Obs)	en Field Obs	0					
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7003	٥	0	0	0	0	0	•	٥	0	۰	0	•	0	0
7001	0	•	0	0	•	۰	•	•	•	•	۰	•	0	0
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Sec.: Male Day(s) Relative to Stort Date

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Vocalization (OF)	(OF) (OF) (OF) (OF)	Vocalization (OF)	mp/kg/day Group 1
eld Obs)	DetClinObs (Open Field Obs)	Decilin	

Individual Animal Detailed Clinical Observations

512						Ž	DetClinObs (Removal from Cage)	ನಾಗ ಕ ್ಷಾಂಗ	(38.					
mp/kg/day Group 2	Handling Reactivity	Handling Reactivity	Handling Reactivity	Handing Reactivity		Vocalization (RC)	Handling Vocalization/Vocalization/Vocalization/Vocalization/ RC) Reactivity (RC) (RC) (RC) (RC) (Closure	Voculization (RC)	Voculization (RC)	Voculization (RC)	Pulpebral Closure	Papebral Closure	Pulpebral Closure	Pulpcbral Closure
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7023	Ф	0	0	0	0	0	0	۰	0	•	0	•	0	•
7024	۰	•	•	0	•	۰	•	•	•	0	۰	•	•	•
7025	o	0	0	0	0	0	0	0	¢	0	•	0	0	=
7026	۰	0	0	•	0	9	•	•	٥	0	•	0	0	0
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7028	0	•	0	0	0	0	0	•	⇒	0	9	0	0	0
7029	0	•	0	0	0	0	۰	0	٥	٥	۰	o	۰	0
7030	c	c	0	_	_	_	-	•	•	•	•	•	•	•

Individual Animal Delailed Cinical Observations

Sex: Male Day(4) Relative to Start Date

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DetClinObs (Removal from Cage)	alton Eye	0	0	•	•	•	0	•	•	•	
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Individual Animal Detailed Clinical Observations

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7026	0	•	0	•	0	0	•	0	۰	0	٥	•	٥	0
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7028	٥	•	0	0	0	0	•	0	٦	٥	0	•	٥	0
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Individual Animal Detailed Clinical Observations

512						Def	DetClinObs (Removal from Cage)	oval from Ca	(38					
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507	0	0	0	0	0	•	٥	0	٥	0	•	•	٥	0
70 <u>7</u>	0	0	0	•	۰	•	•	٥	•	0	0	•	٥	0
207	0	0	0	0	0	•	0	0	0	0	÷	3	Þ	0
7026	0	0	0	٥	0	٥	0	٥	•	0	0	0	0	0
7027	0	•	0	0	•	•	•	0	•	0	0	o	s	•
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Individual Animal Detailed Clinical Observations

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				Determines	Detaillaces (Removal from Cage)	om Cage)					DECIM	Det. inche (Open riela UBS)	eld (JDS)	
mg/kg/day	Respiratory	Respiratory	Respiratory	Respiratory Respiratory Respiratory Respiratory Pupillary		Pupillary	Pupillary	Pupillary	Pupillary	Activity/	Activity/	Activity/	Activity/	Activity/
	Fallen	Lane II	Fallen	E S		Kellex	Z E	X S S S S S S S S S S S S S S S S S S S	Keller	Espon	vvocsal	ESINOS Y	Arousai	Aronsar
	r-	3	F1	<u>ج</u>	•	r-	±	77	82	٥	7	3	2	8
7021	0	0	0	o	o	0	٥	0	0	0	0	•	0	0
7023	٥	0	٥	0	0	0	•	٥	.0	9	>	⇒	0	9
1023	0	0	0	0	0	0	0	۰	0	۰	٥	•	0	0
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7025	0	•	0	c	0	0	0	0	0	٥	a	•	0	=
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7930	0	٥	0	0	0	Ф	5	0	>	0	0	D	0	Đ

Individual Animal Detailed Clinical Observations

512						ď	DetClinObs (Open Field Obs)	en Field Obs	•					
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7022	•	3	٥	0	0	0	٥	0	0	•	5	۰	0	•
7033	٠	0	٥	0	0	-	•	0	0	•	0	0	0	\$
7024	٥	٥	0	0	0	0	٥	0	Ф	•	0	0	0	¢
7025	0	٥	0	0	0	0	•	0	0	•	0	0	0	0
7026	0	٥	٥	٥	0	•	•	0	0	•	0	0	0	0
7027	0	0	0	0	0	٥	•	0	Φ	•	٥	•	0	9
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7030	_	_	c	_	_	_	c	-	Ç	<u>-</u>	•	-	_	=

Individual Animal Detailed Cimical Observations

12					<u> </u>		DetClinObs (Open Field Obs)	en Freid Obs	٤)					
nigikgiday Group 2	Posture	j <u>e</u>	Gait	Gail) je	Carif.	Locanolian Locanialian Locanialian Locanialian Locanolian Defecation Defecation	Locolnotion	Locometion	Locomotion	Locamotion	Deferation	Deferation	Defecation
	38	0	1	2	12	28	o	7	±	21	28	0	4	4
1207	o	٥	٥	0	٥	0	٥	٥	0	٥	۰	0	0	0
7022	٥	0	٥	٥	Ф	0	٥	•	0	٥	Þ	٥	9	۰
7023	٥	0	0	0	0	0	0	•	0	٥	0	٥	0	0
7024	0	0	•	0	٥	0	•	٥	•	٥	0	•	•	٥
7025	٥	0	0	0	٥	0	0	0	0	0	¢	•	0	0
7026	۰	0	0	0	٥	0	•	٥	0	۰	٥	٥	0	٥
7027	٥	•	٥	0	٥	0	•	0	0	٥	0	٥	9	٥
7028	٥	0	0	0	Ф	0	0	•	0	0	0	0	0	0
7029	٥	0	٥	•	۰	0	0	•	0	۰	۰	٥	0	0
2030	¢	c	_	_	4	•	-	_	_	•	ς	•	_	٥

Indisdust Animal Detailed Chilical Observators PSL Study Number 43166 A 28-Day Dielary Study in Rals

513	L					٥	OlinOhe (O	DalChiObs (Oran Field Obs)	با					
						•	(a) management							
mg/kg/day Group 2	Defection	Defection Defection	Urination	Urinstion	Urination	Urination Urination	Urination	Umsual Behaviors	Unusual Behaviors	Unusual Behaviors	Umusual Behaviors		Umanal Vocalization Vocalization Behaviors (OF) (OF)	Vocaliza (OF)
	21	85	0	٢	1	21	82	Q	7	=	12	83	0	7
7021	o	0	0	Ω	0	°	0	0	0	٥	0	0	0	0
7022	٥	÷	٥	٥	0	•	•	0	•	•	>	٥	•	P
207	2	٥	0	0	0	•	•	0	0	۰	0	0	0	0
7024	٥	•	0	0	0	•	•	0	0	0	•	0	0	0
7025	٥	0	0	0	0	0	•	0	¢	٥	=	0	0	c
7026	0	٥	0	0	•	0	•	0	0	0	•	0	0	0
7027	٥	0	٥	0	•	•	۰	٠	0	0	۰	٥	0	0
7028	٥	0	0	0	•	0	0	0	0	0	۰	۵	٥	0
7029	۰	0	0	٥	۰	•	•	٥	\$	0	۰	٥	٥	0
010	_	_	_	•	•	=		¢	¢	0	•	•	•	0

Individual Animal Detailed Clinical Observations

Sex: Male Day(s) Relative to Start Date

212	DetClin	DetClinObr (Open Field Obs)	eld Obs)
mgKg/day Greup 2	Vocalization (OF)	Vocalization (OF)	Vocalization (Vocalization) (Vocalization (OF) (OF) (OF)
	11	21	28
7021	Ð	0	٥
7022	9	0	٥
7023	Đ	0	٥
7024	0	0	•
707	0	0	0
7026	0	۰	0
7027	0	۰	۰
7028	0	0	0
7029	0	۰	•
7030	0	0	0

mg/kg/day	Vocalization	Vocalization (Vocalization) (Vocalization	Vocalization	
Greup 2	(OF)	(OF)	(O)	
	Ξ	21	28	
7021	Ф	0	0	
7022	9	0	0	
7023	Ф	0	٥	
7024	0	•	0	
7025	0	0	0	
7026	0	۰	0	
7027	٥	۰	٥	
7028	0	0	0	
7029	0	۰	0	
7030	0	٥	0	

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> > Sec: Male Day(s) Relative to Start Date

1024						Z	DetClinObs (Removal from Cage)	loval from Ca	(36)					
mg/kg/day Group 3	Handling Reactivity	Handling	Handling Reactivity	Handling Reactivity	Handling Reactivity	Vocalization (RC)	Handling Vocalization Vocalization Vocalization Focalization Reactivity (RC) (RC) (RC) (RC)	Voculization (RC)	Vocalization (RC)	Vocalization (RC)	Palpebral	Palpetral	Pathebral	Pulpebral Closure
	٥	,	±	17	ន	°	۲	Z	151	28	•	7	=	21
7041	0	0	0	a	Q	0	0	0	0	0	0	0	o	Φ
7042	9	0	0	>	\$	٠	•	0	•	•	•	0	>	•
7043	٠	0	0	0	0	٥	0	0	•	•	0	0	•	\$
7044	0	0	0	0	0	٥	0	0	۰	٥	0	0	0	0
70-15	-	0	c	0	0	0	÷	0	•	0	c	0	0	•
7046	٥	٥	٥	•	0	0	٥	0	۰	٥	0	0	0	٥
7047	٥	۰	٥	0	٥	0	۰	٥	Þ	•	٥	0	0	0
7048	0	o	۵	•	0	0	•	0	0	•	٥	0	0	0
5049	0	۰	۰	0	٥	•	٥	٥	•	•	•	٠	0	0
7050	0	0	•	0	0	0	٥	٥	0	0	٥	÷	0	0

Individual Animal Detailed Civical Observations

0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7612 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	ing-kg/day Palpebral Lacrimation Lacrima	DetClinChs (Removal from Cage) Paladem Lacrimation La	Murcus Membrane 0 0 0 0 0 0 0 0
	7045 70 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	791	Clearer Clearer Membranes Membranes	
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0			Closure	

Individual Animal Detailed Circles Observations

1024						Det	DetClinObs (Removal from Cage)	oval from Ca	(36)					
ingkg/day Group 3	Mucous Mucous Membranes Membranes		Safivation	Salivation	Sulivation	Salivation	Salivation	Emuciation	Ensciation	Ernacration	Einaciation	Emuciation	Salivation Salivation Enuciation Emeration Emeration Emeriation Enuciation Pilomeetion Pilomeetion	Piloerection
	£1	82	٥	۲	=	21	328	θ	7	7	21	88	0	7
7011	0	o	0	o	0	0	0	0	0	٥	0	0	0	0
7042	٥	٥	0	•	•	•	•	٥	0	٥	⇒	0	0	9
7043	0	٥	٥	•	0	0	۵	0	0	0	•	ø	0	0
104	•	۰	۰	•	•	•	٥	۰	0	0	۰	0	•	0
7015	•	0	Q.	0	0	0	۰	٥	0	0	•	0	0	0
7046	0	•	٥	0	•	0	٥	•	0	0	0	٥	0	0
7047	٥	0	0	0	•	0	0	٥	0	٥	٥	0	0	0
7048	0	0	0	0	0	0	0	0	0	٥	۰	0	•	0
5049	•	٥	0	•	•	0	٥	0	0	0	•	٥	0	3
2050	_	_	0	c	0	-	•	0	0	0	۰	٥	0	0

1024						Det	ClinObs (Rer	noval from C	age)					
ng/kg/day Group 3	Pilocrection	Pilocrection	Pilocrection	Fur/Skin	Fur/Skm	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Respiratory Pattern				
	14	21	28	0	7	1-)	21	28	0	7	14	21	28	6
70-11	9	0	0	0	0	0	0	0	0	0	0	0	0	0
7042	0	0	0	0	0	0	U	0	U	0	U	U	0	U
70-13	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70-14	0	0	0	ð	0	0	٥	0	0	0	0	0	0	0
70-15	0	0	0	Ð	0	0	0	0	0	0	0	0	0	- 0
7046	0	0	0	0	0	8	0	0	0	0	0	0	0	0
7047	0	0	٥	0	0	0	0	0	l o	0	0	0	0	0
704B	0	0	O	0	0	0	0	0	0	0	0.	0	0	0
70-19	0	0	0	0	0	0	0	0	O O	0	0	0	0	0
7050	0	0	0	0	0	0	0	l 0	ļυ	0	U	U	0	0

1024			•	DetClinOt	s (Removal	from Cage)					DetClin	Obs (Open F	eld Obs)	
ng/kg/day Group 3	Respiratory Paltern	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	D	0
7042	0	0	0	0	Q	0	0	0	0	U	0	0	0	0
7043	1 0	0	0	D	0	0	0	0	0	0	0	0	0	0
7041	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70-15	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
70-17	0	0	0	Q	0	0	0	0	0	0	0	0	0	0
7048	lo	0	0	0	0	0	0	0	0	lυ	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		Ð	Ð	0	lo	0	0	0	0

024			_			D	etClinObs (O	pen Field Ob	s)					
ng/kg/day Group 3	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions	Freemory	Tremors	Tranors	Tremore	Tranors	Posture	Posture	Posture	Posture
7041	0	. 7	14	21	28	0	7	14	21	28	0	7	14	21
7041 7042	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7043	"	0	0	0	0	D	D	o	Ð	0	0	0	0	0
70-14	ا ہ	ò	0	0	0	ō	ŏ	ŏ	o	0	ò	ő	0	o
70-15	0	0	0	0	0	0	0	0	0	o	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
70-19	0	0	0	0	0	0	0	0	0	0	0	Q	0	0
7050	0	o	0	0	υ	0	0	0	0	0	U	0	Ø	0

Individual Animal Detailed Cinical Observations

Sex: Male Day(s) Relative to Start Date

_							DetClinObs (Open Field Obs)	orn Field Obs	0					
mg/kg/day Group 3	Poture	Gail	Cag	Gait	Cast	Cait	Locanotian Locanotian Locanotian Locanotian Locanotian Deferation Deferation	Locomoton	Loconolion	Locomotion	Locomotion	Defecation	Defecation	Defecation
	58	0	7	7	73	28	0	7	7	21	28	0	7	2
7041	٥	0	0	0	0	٥	0	0	0	٥	٥	0	0	0
7042	٥	•	0	0	0	0	•	0	•	•	٥	0	9	۰
7043	0	•	0	0	0	0	0	0	o o	۰	•	0	0	۰
1040	0	0	0	0	0	0	0	0	o	•	٥	0	•	٥
7045	٥	٥	0	0	0	0	٥	0	¢	o	s	0	0	¢
7046	٥	۰	0	0	•	0	٥	0	0	۰	۰	0	0	0
7047	٥	۰	٥	5	0	0	0	0	٥	٥	٥	0	9	0
7048	¢	۰	0	٥	0	0	۰	0	0	٥	٠	0	0	0
7049	۰	•	۰	٥	•	0	۰	0	Þ	9	۰	٥	0	0
7050	Ф	٥	0	0	0	0	•	0	0	_	0	0	0	0

Individual Animat Detailed Cánical Observations

102						ద	Clinobs (Ox	DetClinObs (Open Freid Obs)	_					
mg/kg/day Group 3	Defection	Defection Defection	Urinution	Unimition	Unnution	Urinstien Urination		Unusual Behaviors	Unusual Behaviors	Unusual Behavions	Unusual Behaviors	Unusual Behaviors	Unusual Vocalization Vocalization Behaviors (OF) (OF)	Vocalization (OF)
·														
	23	88	0		3	12	83	Q	7	Ξ	21	38	0	1
7041	0	٥	0	0	0	0	0	o	0	0	0	9	0	0
7042	٥	•	•	0	0	0	0	۰	0	0	÷	⇒	0	Đ
7043	0	•	0	0	0	0	0	0	0	•	•	•	0	0
70 M	٥	•	0	0	•	0	•	•	0	•	•	۰	0	•
7045	÷	•	0	0	0	•	-	•	•	0	•	۰	0	÷
70. 840°	٥	0	0	0	0	•	0	۰	0	٥	۰	•	0	•
7017	۰	0	0	0	٥	0	0	٠	Þ	٥	٠	٥	0	⇒
840 <u>-</u>	٠	•	0	0	0	0	•	Ф	Đ	o	٥	•	0	÷
7019	۰	0	•	•	6	٥	•	٥	•	0	•	٥	0	÷
7050	÷	0	0	٥	٥	0	0	•	0	0	٠	3	0	Þ

Sex: Male Day(s) Relative to Start Date	-	mpkg/day Vocalization Group 3 (OF)	7.	7041 0	7042 0	7043	0 140	7045 0	2046	7047	7048 0	
o Start Date	DetClinObs (Open Field Obs)	Vocalization (OF)	21	0	0	0	0	0	0	0	0	
	eld Obs)	Vocalization Vocalization Vocalization (OF) (OF) (OF)	28	0	۰	0	0	0	0	٥	0	

Proceeding Proceeding Reactivity RC) Proceeding Procedure Proceeding Procedure Proceeding Proceeding Procedure Procedur	Vocalization (RC) (RC) (RC) 0 0 0 0 0 0 0 0	(Clin Osa (Clin	7 14 7 14 0 0 0 0 0	le lå _	21 21 21 21 21 21 21 21 21 21 21 21 21 2	Cape) NI Vocalization Vocalization (RC) (RC) 0 0 0 0 0 0 0 0 0 0 0 0 0	Cope Pulpodraj Pulpodraj		tCfinObs (Removal from	tClinObs (Removal from	(RC) (RC)	7 114	0	0	0	0	0	•	0	0	0	
- &	tending (cactivity 28 28 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	DA Vocalization (RC) (RC) 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Como	CliniOA (Removal fra) (RCC) (RCC)	1/Ocelhazation/Oce	Veralization Vera	VCRelianChe (Removal From Cage) Pulpetral Pulpet		Ď	ŏ	fandling Vocalization (eactivity (RC)		0 0	•	0	0	0	0	0	0	•	
1 1 2	Read	Illing iivity	DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChing DetChi	DecClinObs (Removal from the property Part	DetChinChe (Removal from Cage)	Hints	Description (New Removal from Cage) Pulpoten				Handling Reactivity	22	0	•	0	0	0	•	•	0	2	1
	Handling Reactivity 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Handling Handling Reactivity Reactiv	Haveling Haveling Vocalization Vocal	Description Paralling Pocalization Veralization Pocalization Pocaliza	Parclin/Obs Removal From Cage	Parclinicity Handling Vocalization Vocaliza	Parclinicha Handling Vocalization Voc	Handling Vocalization Pulpebral			Handling Handling Reactivity Reactivity I	Ξ	0	•	•	0	0	0	0	0	•	,
Handling Vocalization Voc	Physterial Closure 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Physterial Closure 2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Physterial Closure 2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Physterial Closure 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Physterial Closure 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Physterial Closure 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1					Patpebral Closure	21	a	9	0	0	0	0	0	0	٥	

Indisidual Animal Detailed Cinical Observations

Membranes Membranes Membranes 0 7 14 0 0 0
Z I I

Individual Animal Detaited Cinical Observations

536						Det	DetClinChs (Removal from Cage)	Ioval क्रिक्स Ca	(36)					
mpkp/day Group 4	Menibranes Menibranes		Salivation	Salivation	Salivation Salivation	Salivation	Sulvation	Enuciation	Enaciation	Епасівноя	Emaciation	Emeciation	Sulvation Emecation Emachino Emachon Emacinion Emeration Piloerection	Pilocrection
	22	82	0	4	Ξ	21	ន	0	t-	7	21	38	0	r
7061	۰	0	٥	0	٥	0		٥	٥	٥	0	0	0	9
7062	٠	0	0	0	٥	٥		۰	9	٠	٥		0	⇒
7063	¢	0	c	٥	0	9	0	٥	٠	0	0	0	0	•
1904	0	0	0	۰	•	Ф	٥	٥	•	0	•	0	0	0
7065	0	0	0	•	0	0	0	0	•	0	÷	-	0	0
7066	0	•	0	•	0	0	0	0	•	0	٠	0	•	0
7907	0	۰	0	٥	0	0	•	•	•	0	۰	0	٥	0
890¿	٥	0	0	0	· 0	0	٥	0	9	٥	0	0	•	0
4002	۰	•	•	•	٥	0	٥	0	0	۰	٥	٥	۰	0
7070	¢	_	_	=	9	•	-	-		•	<	•		٥

individual Animal Detailed Clinical Observations

Sex: Male Day(s) Relative to Start Date

536 ofterday					And and a second second second) Jay	IDLAS (KEN	LARL HOLDS (KENOVE) FOR CARE	age)	and the second second		-	*	The second secon
roup 4	Piloaedion	Pilorection Pilorection	Piloaection	Fur/Skin	Fur/Skin	Furskin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tenes	Musek	5	FurSkin Muscle TorcMuscle TorcMuscle TorcMuscle TorcMuscle Torc Respiratory Pattern
	1	21	28	0	4	7	21	28	0	7	14	21		28
1902	٥	٥	0	٥	0	0	0	0	0	o	0	0	ſ	0
7062	٥	٥	0	•	•	0	۰	٥	0	•	٠	Ð		5
5902	0	0	0	0	•	0	•	0	0	0	0	÷		0
1064	٥	0	•	•	•	0	•	۰	0	0	٥	0		0
7065	0	0	0	0	0	c	0	0	0	0	•	0		5
7066	o	0	0	0	0	0	0	0	•	0	0	0		0
7967	٥	۰	0	•	0	0	0	٥	5	0	0	0		٥
2002	0	0	0	>	0	0	0	۰	۰	5	0	0		0
6902	۰	٥	0	٥	•	٥	0	0	٥	0	0	•		٥
7070	0	٥	0	0	•	0	•	0	•	0	o	0		~

1536				DetClinObs	DetClinObs (Removal from Cage)	om Cage)					DetClin	DetClinChs (Open Field Obs)	ield Obs)	
mg/kg/day Group 4	Respiratory Pattern	Respiratory Patteni	Respiratory Pattern	Respiratory Respiratory Populiary Pattern Pattern Pattern Reflex	-	Pupillary Reflex	Pupillary Rellex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal

	r-	2	1.	38	0	r	ž	21	82	0	7	3	177	78
1901	0	0	0	0	o	0	0	٥	0	0	\$	Đ	o.	÷
7062	٥	0	0	Þ	•	٥	0	٥	0	0	•	5	0	٠
7063	٥	0	0	0	0	٥	0	٥	0	0	۰	0	0	⇒
7065	¢	•	0	¢	•	٥	0	٥	0	0	•	C	0	¢
7065	0	0	o	o.	0	a	0	0	0	0	۰	0	0	=
7086	۰	0	0	0	•	•	0	0	0	0	۰	0	0	•
7967	٥	0	0	φ	0	٥	0	0	٠	0	۰	0	0	⇒
7068	٥	0	0	ə	0	0	~ 0	0	•	0	•	0	0	•
7069	۰	٥	0	۰	0	۰	0	0	÷	0	•	0	•	\$
7070	٥	0	0	۰	5	0	9	0	÷	0	-	٥	0	Þ

Individual Animal Detailed Cénical Observations

Sex: Male Day(s) Relative to Start Date

36						5	HCIMODE (O	DelClatObs (Open Field Obs)				- 1	
Coup 4	Convulsions	Convulsions (Convulsions Convulsions Convulsions Tranons	Convulsions	Carrubians	Contubions	franors	Tremas	Tranons	Tremors	Тистог	Poture	 Posture	
	0	_	ż	23	8	0	7	ĭ	12	85	0	7	7 14
1902	9	0	0	0	0	0	0	0	0	0	0	 0	0 0
7062	٥	0	0	٥	0	۰	0	0	•	•	~	 o	0
7063	o	0	0	0	0	0	0	0	•	0	٥	 ٥	0
1064	۰	0	•	0	•	•	0	0	•	٥	0	0	0 0
7065	Þ	c	0	0	0	<u> </u>	0	0	•	0	0	o	0
7066	٥	٥	0	0	0	0	0	0	0	0	0	 0	0 0
7907	۰	٥	0	0	0	٥	•	٥	Þ	•	0	0	0
7068	•	٩	0	9	0	0	0	0	•	•	0	0	0 0
4907	.	٥	٥	0	0	0	0	•	•	•	٥	0	0
07.07	۰	•	0	•	0	•	•	•	Φ	0	•	-	0 0

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> PSL Study Number 43168 A 28-Day Dietary Study in Rats

> > Sex: Male Day(s) Relative to Start Date

Locomotion Locomotion Locomotion Locomotion Defecation | Defecation | Defecation DelClinObs (Open Field Obs) Sait Š Ē Gail Ē Posture 1905 2907 1063 1065 1066 1069 1069 0707 1536 ing/kg/day Group i

Individual Animal Detailed Clinical Observations

Sec: Male Day(s) Relative to Start Date

1536						ď	etClinObs (O	DetClinObs (Open Field Obs)	1					
ing/kg/day Group 4	Defecation	Defection Defection Untalion	Urination	Crimition	Unitedion	Urination	Urnistion Urnation	Unusual Beliavions	Unisual	Unusual Behaviors	Uracus] Behaviors		Unusual Vocalization (OF) Behaviors (OF) (OF)	Vocalization (OF)
	21	57	0	7	17	21	38	9	1	1	23	82	0	۲
1901	0	0	0	0	0	0	0	٥	0	0	0	0	9	٥
7062	ò	0	0	۰	•	۰	•	۰	•	5	9	\$	٩	0
7063	٥	0	0	0	0	٥	0	•	۰	0	0	0	0	\$
7064	0	•	•	0	0	۰	•	•	•	٥	0	0	0	0
7065	0	0	0	0	0	0	0	0	•	0	0	0	0	c
2066	•	0	0	0	•	•	0	0	•	0	ò	0	•	0
7067	٥	۰	٥	0	0	۰	0	0	۰	٠	٥	0	•	¢
7068	•	٥	0	٥	0	0	•	0	٥	\$	0	0	0	0
7069	٥	•	٥	0	0	•	۰	6	>	•	٥	0	0	0
7070	0	0	0	•	•	•	۰	0	•	0	•	o	0	0

Sex: Male Da	Day(s) Relative to Start Date	o Start Date	
1536	DetClin	DetClinObs (Open Field Obs)	eld Obs)
mp/kg/day Group 4	Vocalization (OF)	Vocalization (OF)	(OF) (OF) (OF)
	3	77	28
1901	0	9	0
7062	0	٥	0
7063	٥	٥	0
7061	•	0	0
₹902	•	o	0
7066	•	0	0
7067	٥	0	0
2002	٥	0	٥
7069	Φ	0	٥
0707	=	_	0

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date DetClinObs (Removal from Cage) mg/kg/day Group l Handling Handling Handling Handling Reactivity Reactivi Palpebrai Palpebral Palpebral Closure Closure Closure 2) υ o o

288

Individual Animal Detailed Clinical Observations

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

						DetC	linObs (Rem	DetClinObs (Removal from Cage)	(agi					
mpka/day Group 1	Palpetral Closure	Lucrimation	Lectimatio	Papetral Lacrimation Lacrimation Lacrimation Lacrimation Closure	Lacrimation	Lacrimation). (a) (a	Eye	Ří	ř	Membranes	Mucous Mucous Membranes Membranes Membranes	Mucous
	28	0	1	14	31	82	٥	7	M	21	28	0	7	2
7011	٥	0	0	0	0	0	٥	•	0	٥	0	Q	٥	0
7012	٥	٥	0	0	۵	0	۰	0	0	Φ.	Þ	۰	•	0
7013	0	0	٥	ó	0	0	0	٥	0	۰	۰	٥	0	o
701.4	۰	•	0	0	۰	0	•	0	•	•	۰	•	0	0
7015	Ф	0	•	0	0	٥	0	٥	0	•	0	0	0	0
7016	0	0	٥	0	•	•	0	•	0	0	۰	۰	•	0
7017	0	0	٥	0	0	٥	0	٥	٥	٥	۰	0	>	•
7018	٠	0	٥	<u> </u>	0	o	0	0	•	0	٥	0	9	0
610 ′	٥	0	٥	÷	0	۰	٥	•	•	0	۰	0	٥	Ð
0000	•	•	c	=		<	٠	•	<	٠	٠			5

Individual Animal Detailed Clinical Observations

0)ŠĘ	DetClinObs (Removal from Cage)	oval from Ca	(%)					
rngskodisj Group 1	Munkranes Membranes Membranes Membranes	Menbranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emaciation	Ensciation	Emuciation	Emaciation	Emaciation	Salivation Emeriution Emeriation Emeriation Emeriation Phorocetion Phoroceton	Pilorection
	21	38	0	7	7	12	82	0	r-	2	12	8	0	۲۰
1107	٥	0	0	٥	٥	٥	0	0	٥	o	0	a.	0	۰
7013	٥	0	٥	>	٥	~	0	٥	-	•	0	-	•	۰
7013	c	0	0	0	٥	٥	0	0	0	0	0	٥	٥	٥
7014	۰	0	•	0	٥	¢	0	0	0	0	0	٥	٥	•
2012	۰	0	0	0	0	0	0	0	•	0	0	Đ	0	0
7016	۰	٥	0	0	•	٥	0	0	•	0	0	٥	•	0
101	۰	0	٥	0	٥	٥	0	0	٥	0	0	٥	٥	٥
7018	٥	0	0	0	0	٥	0	0	•	⇒	0	0	0	٩
6102	۰	0	٥	•	0	۰	0	0	٥	٥	0	٥	•	0
7020	۰	٥	0	0	0	0	0	0	٥	-	0	0	0	0

Individual Animal Detailed Cinical Observations

U						DetC	DetClinObs (Removal from Cage)	oval from Ca	180)					
mp/kg/day Group I	Pilogrection	Piloerection	Pilogrection Pilogrection Pilogrection Fiu/Skin	(annual annual a	Fur/Skin Fur/Skin	Fur/Skin	Fur/Skm	Fur/Skin	Muscle Tone.	Fur/Skin Mustle ToneMustle ToneMustle ToneMustle Tone Repitatory Pattern Pattern	Muscle Tone	Muscle Tone	Muscle Tone	Respiratory Pattern
	1	21	138	0	7	14	23	28	¢	7	7	12	28	0
7011	٥	0	0	0	0	•	0	0	٥	0	0	9	0	÷
7012	٠	0	0	\$	۰	_	>	0	÷		•	2	0	⇒
7013	\$	0	•	0	0	٥	0	0	0	0	۰	•	0	=
7014	۰	0	0	٥	•	•	0	0	0	•	۰	0	0	•
7015	٥	0	0	0	0	•	0	0	¢	0	•	0	c	¢
7016	۰	0	0	0	•	•	•	0	0	•	۰	0	0	\$
7017	۰	•	0	0	•	•	0	0	÷	•	•	0	0	÷
7018	•	0	0	<u></u>	0	٥	0	0	9	0	•	0	0	⇒
7019	٥	•	۰	٥	•	٥	0	0	٥	5	۰	٥	0	\$
0002	•	_	~~~	_	_	_	_	•	9	=	•	=	_	•

•				DetClinOb	s (Removal	from Cage)					DetClin	Obs (Open Fi	eld Oos)	
ng/kg/day Groep 1	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Pupillary Reflex	Pupitlary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	14	21	28	0	7	[4	21	28	0	7	1-1	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	O	0	O.	U	0	υ
7013	D	0	0	0	0	0	0	0	0	0	0	0	0	0
7014	0	0	0	0	0	0	0	1 0	0	0	Đ.	0	0	0
7015	0	0	0	0	0	0	Ð	0	0	0	0	0	0	0
7016	0	0	0	9	0	0	Ð	0	0	0	0	0	0	0
7017	0	0	0	0	Q	0	0	0	0	0	0	0	0	0
7018	0	0	0	O	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	o	0	0	0	D	0	0	0	0	0	D	U

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						č	DetClinObs (Open Field Obs)	en Field Obs						
me/kg/day Group 1	Convulsions	Convubions	Convulsions	Convulsions	Convulsions Convulsions Convulsions Convulsions Trentors	Tranors	Tremors	Fremory	Гепот	Tranors	Рошге	Posture	Porture	Posture
	0	,	±	21	38	0	r.	2	21	28	0		3	12
7011	0	0	٥	0	٥	0	0	o	٥	٥	0	٥	0	9
7012	•	0	0	0	٥	٥	0	÷	9	٥	•	•	0	Þ
7013	\$	0	•	0	0	•	0	٥	0	0	•		0	•
7974	•	0	•	•	0	٥	•	•	•	0	٠	С	0	0
7015	0	٥	0	•	0	0	0	0	•	0	•	0	0	0
7016	0	0	0	•	0	0	•	0	•	0	•	0	٥	Đ
7017	0	٥	۰	٥	0	0	۰	0	٠	0	•	•	•	0
810/	0	•	•	0	0	0	۰	0	0	0	0	Φ	٥	0
7019	0	٥	٥	٥	٥	0	۰	•	٥	٥	0	۰	٥	0
2020	c	•	-	<u>-</u>	_		4		\$	4	_	ς	•	=

Individual Animal Detailed Clinical Observations

Poblar Cail Cail Cail Cail Cail Cail Cail Comerten Locemeten Locemet							Ω	etClinObs (O	DetClinObs (Open Field Obs)						
18 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	okap 1	Podure	Cart	Calt	Sail.	15 		Locomotion	Loconotion	Locomotion	Loconacion	Locamotium	Defectation	Defecation	Defreation
7011 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		18	0	1	7	31	28	0	7	Ξ	21	28	0	ŀ	I
7012 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7011	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 0 0 0 0	7012	۰	0	٥	٥	0	۰	0	•	•	٥	•	o.	9	۰
7014 7015 7016 7016 7017 7018 7019	2013	0	0	9	0	0	0	0	0	•	÷	0	0	0	0
7015 6 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	101	0	0	0	0	0	0	•	•	o	٥	0	0	0	0
7016 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7015	¢	0	o	0	0	0	0	0	÷	\$	0	٥	0	0
7017 0 0 0 0 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	Đ
7018 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7017	9	0	0	0	0	0	0	0	٥	٥	٥	0	0	Φ
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7018	٥	0	0	0	0	0	0	0	٥	-	•	0	0	9
0 0 0 0 0 0 0 0 0	7019	0	•	0	0	0	•	•	0	٥	-	٥	0	0	o
, , , , , , , , , , , , , , , , , , , ,	7020	0	•	0	•	•	0	\$	0	•	^	•	0	0	o

Individual Animal Detailed Clinical Observations

						Ę	DetClinObs (Open Field Obs)	nen Field Obs						
mg/kg/day Grosp 1	Defection	Defecation Urination	Urination	Urinstica	Urination Urination Urination Urination Behaviors	Urination	Urination	Umsual Behaviors	Unusual Behavions	Unusual Behaviors	Unusual Behaviors	Unusuil Behaviors	Unusuul Vocalization Vocalization 3ehaviors (OF) (OF)	Vocalizution (OF)
	21	87	٥	,	3	12	238	Þ	,	±	23	38	o	7
7011	0	٥	0	o	0	0	0	٥	٥	0	9	0	٥	0
7012	٥	,	•	Ş	0	•	•	•	•	0	9	0	٥	0
7033	0	٥	•	•	0	٥	0	0	٠	0	٥	0	٥	0
7014	0	٥	•	0	0	•	•	0	•	0	٠	0	0	0
7015	0	0	•	o	0	•	•	0	¢	0	٥	0	0	0
2016	0	0	0	٠	0	•	۰	0	•	0	٥	0	٥	0
7017	٥	۰	0	٠	0	•	•	0	0	0	0	0	٥	0
7018	0	٥	0	٥	0	0	•	0	0	0	٥	0	٥	0
7019	9	۰	0	۰	٥	۰	۰	0	٥	0	٥	٥	۰	0
2070		-	•	•	•	•	•	•	<	•	•	5	•	5

294

Date
to Stert
Cative 1
Day (s) I
Female

Sex: Female	Day(s) Relative to Start Date	e to Start Dat	
0	Detclin	DetClinObs (Open Field Obs)	eld Obs)
ing/kg/day Group I	Vocalization (OF)	Vocalization (OF)	ocalization/Vocalization Vocalization (OF) (OF) (OF)
	7	7.	28
1102	0	0	0
7012	۰	0	0
7013	٥	0	0
7014	•	0	0
7015	0	0	0
7016	•	0	0
7017	۰	٥	0
7018	۰	0	0
7019	۰	٥	0
7020	۰	0	0

Individual Animal Detailed Clinical Observations

512						Det	DetClinObs (Removal from Cage)	wal from Ca	(38					
nışıkş/day Group 2	Handing	Handing	Harding	Handing	Handling	Vocalization	Handling Woralization Woralization Woralization Woralization Pulpebral Reaction (RC) (RC) (RC) (RC)	Vocalization	Voculization	Vocalization	Palpebral	Pulpebrai	Patpebral	Pulpebral
	•	`			`	Ì	Ì		Ì					
	Ω	۲	7	2.	38	o	r	ī	17.	82	0	7	=	22
7031	0	0	0	0	0	æ	٥	0	•	0	٥	0	0	9
7032	5	•	•	٥	0	Ф	9	0	•	0	•	5	•	3
7033	0	۰	0	0	0	٥	•	0	۰	0	٠	0	0	0
7034	0	•	0	•	0	0	•	•	•	0	۰	¢	¢	0
7035	0	0	0	0	٥	0	0	0	•	0	•	φ	¢	0
7036	0	۰	0	•	0	0	•	0	•	0	٥	Φ	0	0
7037	0	•	0	0	٥	0	•	0	⇒	٥	٥	۰	0	0
7038	0	٥	0	0	0	0	φ	0	9	0	0	Ф	0	0
7039	٥	•	٥	0	0	0	•	0	٥	0	٥	ç	٥	0
7040	0	٥	•	•	0	0	\$	0	٥	0	0	٥	0	_

296

Individual Animal Detailed Cinical Observations

					DetC	ClinObs (Ren	DetClinObs (Removal from Cage)					***************************************	
Lucrimation Lass	<u> </u>	imakion	Lestrimation Lactimation Lactimation Latrimution	Lacronation	Lacrimation	ชั้	å	ž	ស្ន័	<u>پ</u> ر	Membranes	Marubranes Membranes Membranes	Mucous
Đ		7	7	23	28	0	7	Ž	17	28	0	7	4
Q	L	0	0	0	0	0	0	0	٥	÷	0	0	0
		O.	0	•	0	-	0	0	<u>-</u>	0	٥	0	•
•		0	٥	٥	0	٥	ø	0	•	0	0	0	0
•		0	•	۰	0	٥	Ф	0	0	0	٠	o	0
0		0	٥	0	0	0	0	¢	0	•	۰	0	<u> </u>
0		0	٥	٥	•	0	0	•	•	0	٥	٥	\$
0		0	•	0	۰	•	٥	۰	•	•	Ç	0	⇒
0		0	0	0	0	0	0	•	•	0	0	0	\$
۰		0	٥	0	•	0	0	۰	•	0	0	0	-
٥		0	0	0	0	0	0	0	0	0	٥	0	9

Individual Animal Detailed Clinical Observations

512						Del	ClinObs (Ren	DetClinObs (Removal from Cage)	(36)					
nipkg/day Group 2	Membranes	Menibranes Membranes	Salivation	Salivation	Salivation	Salvatica Salvation Emaciation Enaciation Enaciation Emaciation Emaciation Phocrection Phocrection	Sulivation	Emactation	Emaciation	Emaciation	Enaciation	Enscialon	Piloerection	Piloaection
	12	288	0	4	2	5	82	o	7	=	21	82	0	1.
7031	2	٥	٥	٥	0	0	٥	0	٥	0	٥	0	٥	0
7032	٥	0	0	٥	0	0	۰	•	0	Þ	5	•	9	0
7033	0	0	0	0	•	0	٥	0	0	Þ	0	•	0	9
7034	٥	0	•	0	۰	•	•	0	0	٠	0	•	0	0
7035	Ф	0	0	0	0	0	0	0	0	•	0	•	0	0
7036	۰	•	0	0	0	•	•	0	0	0	•	٠	0	0
7037	٠	٥	0	•	0	0	0	0	0	0	•	9	0	⇒
7038	0	•	٥	٥	0	0	-	0	0	0	•	0	0	⇒
7039	٥	•	0	•	٥	۰	•		٥	0	۰	۰	٥	Đ
7040	0	0	0	0	0	0	۰	0	o	0	3	٥	٥	5

12						Det	ClinObs (Ren	noval from C	age)					
ng/kg/day Iroup 2	Pilocrection	Pilocrection	Piloerection	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Musele 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	Ð	0	0	U	υ	0
7033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7034	0	0	٥	0	0	0	0	0	0	0	0	0	٥	0
7035	0	0	0	0	0	0	3	3	0	0	0	0	0	Ð
7036	0	0	0	0	0	0	Ü	٥	0	0	0	0	0	0
7037	0	0	0	0	Q	0	0	0	0	0	0	0	Q	0
7038	0	0	0	0	0	0	0	Ð	0	υ	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	Ð	0	O	0		0	0

PSL Study Number 43168 A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date ing/kg/day Group 2 DetClinObs (Removal from Cage) DetCfinObs (Open Field Obs) Respiratory | Respiratory | Respiratory | Pupillary Pupillary Pupillary Reflex Activity/ Activity/ Activity/ Pupillary Pupiliary Activity/ Activity/ Reflex Reflex Pattern Pattern Pattern Reflex Reflex Arousal Arcusal Arousal Arousal Arousal 1-1 D υ

Individual Animal Delaited Clinical Observations

613						ľ	4ChiObs (Q	DetClinObs (Onen Field Obs)	_					
mg/kg/day	Convulsions	Convulsions	Convulsions	Convulsions Convulsions Convulsions Convulsions Transons	conditions	Tranors	Tremay	Ттапогу	Tremors	Trans	Posture	Posture	Posture	Posture
roup 2														
	0	4	ı	21	88	o	٢	1	12	28	0	r.	14	21
7031	0	0	0	٥	0	0	0	0	٥	0	0	0	٥	0
7032	0	0	0	•	•	0	•	•	٥	0	۰	•	٥	Ð
7033	0	0	0	•	•	Ð	0	•	•	0	0	•	Ģ	\$
7034	٥	0	0	0	Φ	0	•	•	•	0	0	0	0	0
7035	0	0	0	٥	0	0	0	0	•	0	0	0	•	¢
7036	٥	0	•	٥	•	0	0	0	•	۰	0	0	0	0
7037	٥	٥	•	•	0	٥	٥	•	٥	۰	0	۰	0	0
7038	٥	သ	0	9	0	0	0	0	0	•	3	0	0	Ð
7039	o	٥	•	•	0	0	•	•	٥	•	0	٥	0	÷
7010	0	٥	0	•	0	0	•	•	0	٥	3	0	0	9

Individual Animal Detailed Cinical Observations

Sex: Female Day(s) Relative to Start Date	Day(s) Relativ	re to Start Dal	٥											
512						I	DetClinObs (Open Field Obs)	nen Field Obs	0					
mg/kg/day Group 2	Posture	Gait	Gait	Gail	Saji S	Gait	Locomotion Locomotion Locomotion Locomotion Deferation Deferation Deferation	Locomotion	Locomotion	Locomotion	Locanotien	Defecation	Deferation	Defecution
	28	ə	7	77	21	28	0	7	Ξ	21	28	0	7	7
7031	٥	0	0	0	0	0	٥	0	0	0	0	0	Ð	0
7032	٥	٥	0	٥	٥	0	٥	٥	٥	٥		٥	٥	0
7033	0	٥	0	0	0	0	o	0	0	0	0	0	0	0
7034	0	0	0	•	o	0	•	0	0	•	•	•	0	٥
2035	٥	0	0	0	¢	0	•	٥	0	Φ	0	۰	0	0
7036	0	0	0	•	0	•	0	۰	0	•	0	•	0	o
7697	٥	0	0	0	٥	٥	0	0	0	٥	0	٠	0	۰
7038	9	0	٥	0	٥	0	0	۵	0	•	•	0	0	۰
7039	۰	0	٥	0	0	•	0	٥	0	•	•	0	9	•
7640	٥	0	0	٥	0	0	•	0	0	•	0	0	0	٥

Individual Animal Detailed Cinical Observations

딘						Φ	etClinObs (C	DetClinObs (Open Field Obs)	•					
gAgday coup 2	Detection	Defecation Defecation Unitalion Unitalion Unitalion Unitalion	Urinstian	Urinution	Urination		Urination	Unusual Behaviors	Umunal Behavions	Unusual Behaviors	Unosual Behaviors	Unusual Behaviors	Unusual Vocalization Vocalization Behaviors (OF) (OF)	Vocalization (OF)
	ï	38	o	7	2	21	38	0	7	7-	21	85	0	1
7031	٥	٥	0	0	0	0	0	0	0	0	9	0	0	0
7032	٥	9	0	•	0	9	•	0	0	•	•	3	0	9
7033	0	0	0	0	0	0	\$	0	0	0	۰	\$	0	0
707	0	•	0	0	•	•	o	•	0	0	•	¢	0	•
7035	0	0	0	0	0	•	0	0	0	0	÷	•	Ð	c
7036	٥	0	0	0	٥	•	0	0	•	0	0	•	0	0
7037	٥		0	Þ	٥		0	0	٠	٥	0	٥	0	0
7038	٥	0	٥	0	0	٥	0	0	•	÷	0	0	0	\$
402	٥	0	٥	0	0	۰	0	0	٠	٠	0	0	0	Ф
7040	0	0	0	0	0	0	٠	•	9	\$	0	0	0	O
										The second secon				

Individual Animal Detailed Clinical Observations

512	DetClin	DetClinOhr (Open Field Ohs)	eld Obs)
mgxg/day Group 2	Vocalization (OF)	Voculization (OF)	(OF) (OF) (OF)
	H	21	28
7031	0	0	0
7032	٥	0	0
7033	0	٥	0
7034	0	0	0
7035	0	0	0
7036	0	0	0
7037	٥	٥	0
7038	٥	0	٥
7039	٥	٥	0
7040	٥	0	۰

Vocalization Vocalization Vocalization (OF) (OF) (OF)	21 28	0 0	0	0	0	0 0	0	0	0	0	0
Vocalization V (OF)	ı	θ	٥	0	•	0	0	0	0	٥	٥
mgkg/day Group 2		7031	7032	7033	7034	7035	7036	7037	7038	6502	7040

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1024						Det	Det ClinObs (Removal from Cage)	loval from Ca	(8¢)					
mg-kg/day Group 3	Handling Reactivity	Handling Reactivity	Handling Reactivity	Hardling Reactivity		Handhing Vocalization/Vocalization/Vocalization (RC) (RC) (RC) (RC) (RC) (RC) (RC) (RC)	Voculization (RC)	Vocalization (RC)	Vocalization (RC)	Vocalization (RC)	Pulpebral Closure	Papderal Closure	1	Palpebral Closure
	0	1-	7	77	85	0	r	14	21	38	0	7		14
7051	0	0	0	0	0	0	0	0	0	0	0	0		0
7052	٥	0	•	0	0	٥	٥	۰	۰	0	\$	÷		⇒
7053	٥	0	0	0	0	ò	0	0	•	0	0	9		0
7054	٥	0	0	9	•	۰	0	0	•	0	۰	0		Φ
7055	٥	0	0	0	0	•	0	0	•		9	0		-
7056	٥	0	0	٥	0	۰	0	0	•	0	0	0		0
7057	٥	•	٥	٥	٥	٥	0	0	•	3	٥	Đ		2
7058	÷	•	0	٥	0	0	0	0	•	0	0	Φ		٥
7059	٥	0	٥	٥	٥	•	0	٥	•	٥	0	٥		0
0902	0	0	0	0	0	•	0	0	•	•	0	0		٥

306

Individual Animal Detaited Cinical Observations

024						DetC	linObs (Rem	DetClinObs (Removal from Cage)	gc)					
ing/kg/day Group 3	Palpebral Closure	Lacrimation	Physical Lacrimation Lacrimation Lacrimation Lacrimation Lacrimation Chosure	Lucrimation	Lacrimation	Lacristuation	र्भेन	Eye	Eye	3/g	Бус	Mucous Membranes	Mucous Mucous Mucous Membranes Membranes	Mucous Membranes
	38	P	7	7.	31	28	•		7	12	28	0	٢	7
7051	0	٥		0	٥	0	•	0	0	o	٥	o	ō	0
7052	٥	٥	0	0	٥	•	۰	•	0	•	Đ	•	٥	0
7053	٥	٥	0	0	o	0	۰	0	0	¢	0	۰	0	0
7054	٥	۰	0	0	0	•	•	•	0	0	0	•	o	0
202	0	0	0	0	٥	c	•	0	0	0	0	۰	٥	0
7056	0	0	0	0	٥	•	•	0	0	0	0	•	0	0
7057	۰	0	0	0	٥	•	٥	•	0	۰	0	•	٥	Đ
7058	0	0	0	0	٥	0	•	0	0	۰	0	•	0	0
7059	0	٥	0	0	٥	•	٥	٥	٥	٥	٥	٥	٥	0
7060	٥	c	0	0	0	0	•	0	٥	0	0	•	0	0

024						Det	ClinObs (Ren	noval from Ca	ige)					
ng/kg/day Group 3	Mucous Membranes	Mucous Membranes	Salivation	Salivation	Salivation	Salivation	Salivation	Emuciation	Emaciation	Emaciation	Emaciation	Emaciation	Pilocrection	Pilocrection
	21	28	0	7	14	21	28	0	7	14	21	28	0	7
7051	0	0	0	D	0	0	0	0	0	0	0	0	0	0
7052	0	0	0	0	0	0	0	0	0	v	0	0	0	0
7053	0	0	0	υ	0	0	0	0	0	0	0	0	0	0
7054	0	0	0	0	ð	0	0	0	0	0	0	0	0	0
7055	0	0	O-	0	0	0	0	0	0	0	0	0	0	0
7056	0	0	0	0	Ð	0	0	0	0	0	0	0	0	0
7057	0	0	0	0	0	0	0	0	Ð	0	0	υ	U	0
7058	0	0	0	0	0	0	0	0	Ð	0	0	Ü	O	0
7059	0	0	Q.	0	0	٥	0	0	0	0	0	0	0	0
7060	0	G G	0	0	Ð	0	0	0	0	0	O	υ	Ð	0

Individual Animal Detailed Cinical Observations

							Det	ClinObs (Rem	DetClinObs (Removal from Cage)	(SE)					
21 28 0 1.7 1.4 2.8 0 1.4 2.1 2.8 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Pilon	ection	Piocrection	Piloerection	Fur/Skin		Fur/Skin	Fur/Skin	Fur/Skin	Nuscle Tone	Muscle I one.	Muscle Tone	Mwele Tone	Muscle Tone	Respiratory Pattern
		±	75	28	0	7	14	21	28	o	4	H	21	28	0
	l	0	٥	0	0	0	0	٥	٥	٥	0	0	0	-	0
		0	2	•	9	0	0	۰	0	٥	0	0	0	>	0
		0	٠	0	0	•	0	•	0	0	0	0	0	Φ.	0
		0	۰	•	•	0	0	•	•	•	0	0	c	0	c
		0	0	-	0	0	0	•	0	•	0	0	÷	•	0
		0	٥	0	0	0	0	•	•	•	0	0	٥	Φ	0
		0	٥	0	0	٥	0	•	0	0	0	0	0	-	0
		2	9	0	9	0	0	Φ	0	0	0	0	o	٥	0
		0	٥	0	0	٥	0	•	0	٥	0	0	٥	٥	9
		0	٥	0	0	٥	0	٠	9	0	0	0	Þ	⇒	0

Individual Animal Detailed Clinical Observations

				100					ľ					
8				Detectino	Detc.incbs (Removal from Cage)	rom Cage)					DetCim	DetClinClos (Open Field Obs)	eld Obs)	
mgkg/day Group 3	Respiratory Pattern	Respiratory Pattern	Respiratory Pattern	Respiratory Respiratory Respiratory Pattern Pattern Pattern	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	r	7	21	82	0	r	2	a	R	0	7	1	21	28
1602	0	0	0	0	0	0	0	0	٥	0	0	0	0	0
7052	۰	۰	0	٥	0	0	•	٥	•	0	٥	٥	0	0
7053	0	0	0	0	0	0	•	0	0	0	0	٥	0	0
20%	0	0	0	0	•	0	Φ	٥	•	0	٠	9	0	0
7055	0	0	0	c	•	0	0	•	٥	0	٥	0	0	c
7056	0	0	0	٥	0	0	0	0	٥	0	•	0	٥	0
7057	٥	0	0	۰	٥	٥	0	٥	۰	0	٠	٥	۵	0
7058	0	0	0	2	0	٠	0	0	٠	3	0	0	¢	⇒
50.07	٠	0	0	٥	0	0	٥	0	۰	٥	0	0	0	•
0902	0	¢	0	0	0	0	0	0	0	0	٥	0	0	\$

Individual Animal Detailed Clinical Observations

Convulsions Tremos Tremos	Titerinosa Tit
Tremos Posture	Tremos Posture Posture
Tremos Posture	Tremos Posture Posture
28 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Tremors Festure Posture 28 0 7 0
	Posture 7 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

Individual Animal Detailed Clinical Observations

1024						E	DetClinObs (Open Fiteld Obs)	pen Field Obs	_					
ng/kg/day Group 3	Posture	<u>.</u>	Gest	Çu	Gait	Gait	Locanotian Locanotian Locanotian Locanotian Defection Defection Defection	Loconolon	Loconolion	Locomotion	Locomotion	Defecation	Delecation	Deferation
	85	0		14	2	28	0	7	#	21	28	0	4	2
7051	٥	٥	0	0	0	0	0	0	0	٥	0	0	0	0
7052	۰	•	0	•	0	٥	٥	0	•	Þ	٥	0	0	9
7053	0	0	0	0	0	0	0	0	•	\$	٥	0	0	۰
7054	٥	۰	0	•	•	0	۰	0	•	•	0	0	•	•
7055	0	0	c	0	0	0	¢	0	-	Φ	٥	0	0	0
7056	٥	•	٥	0	0	0	•	0	0	۰	0	0	0	0
7057	٥	0	۰	٥	٥	٥	٥	٥	٥	•	•	٥	0	0
7058	0	•	٥	0	0	0	0	ð	0	0	٠	0	0	٥
7059	•	0	٥	•	0	0	۰	•	0	0	٥	٥	٥	0
0902	٥	0	0	•	0	0	9	۰	0	•	•	0	0	0
•		_		_	-	•	-		-	-		,		

024						17	etClinObs (C	pen Field Ob	s)					
ng/kg/day Group 3	Defection	Defecation	Urination	Urination	Urination	Urination	Urination	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	31	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
7032	0	0	O	υ	0	0	0	v	ļυ	O	0	Ų	Q	Ų
7053	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7054	0	0	٥	0	0	0	0	0	0	0	0	0	0	0
7055	0	0	0	0	0	0	0	Ð	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	υ	0	0	0	0	0	0	ę	0	Q	U
7058	0	0	0	0	0	Ü	0	0	0	0	0	0	0	0
7039	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7060	0	0	0	0	0	Ð	0	0	0	0	ø	O	0	0

Individual Animal Detailed Cinical Observations

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4 (9-1/d)	
	ı
	- 1
	- 3
	- 1
	•
	- 3
	- 1
	- 1

1024	DetClin	DetClinObs (Open Field Obs)	eld Obs)
ing/kg/day Group 3	Vocalization (OF)	Vocalization (OF)	ocalization Vocalization Vocalization (OF) (OF)
	÷	21	28
1502	0	0	ó
7052	•	0	0
7053	0	0	0
705	•	0	0
7055	0	0	0
7056	0	Ó	0
7057	۰	٥	٥
2028	•	0	0
4020	•	٥	٥
2060	٥	٥	٥

Individual Animal Detailed Cinical Observations

386						Dett	DetClinObs (Removal from Cage)	noval from Ca	(SE)					
grkg/day roup 4	Handing Reactivity	Handing Reactivity	Handing Reactivity	Handling Reactivity	Handling Reactivity	Haidling Vocalization Vocalization (Vocalization) Reactivity (RC) (RC) (RC)	Vocalization (RC)	Vocalization (RC)	Voculization (RC)	Vocalization (RC)	Pulpebral Closure	Papetral	Palpebral Closure	Pulpebral Closure
	0	7	7	21	87	0	-	7	21	38	0	7	2	21
7071	0	٥	٥	٥	0	0	0	0	0	0	0	=		0
50.7	Φ	0	٥	2	0	o	<u> </u>	0	>	0	•		•	÷
7073	0	٥	٥	٥	0	•	_	0	•	0	٥	0	0	0
7074	0	0	٥	•	0	•	•	•	۰	0	۰	0	•	0
7075	0	•	0	٥	0	0	<u> </u>	0	•	0	۰	0	•	c
7076	•	•	0	٥	0	0	•	0	•	0	•	•	•	0
7077	٥	0	٥	0	٥	0	۰	0	٥	0	•	٥	٥	0
87.07	0	0	0	0	0	0	۰	0	Ф	0	٠	0	۰	0
7079	٥	٥	٥	٥	0	0	•	0	٥	o	0	•	۰	0
1080	c	9	_	•	=	_	-		=	_	=	_	•	-

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1536						DetC	TinObs (Ren	DetClinObs (Removal from Cage)	(3g)					
nigkg/day Grœup 1	Palpetral Closure	Palpebral Larmnation Larmnation Larmnation Closure	Lacrimation	Lacrimation	Lacrimation	Lacrimation	š	ši	Eye	3/jq	š	Murous Membranes	Murous Murous Murous Membranes Membranes	Membranes
	82	0	7	71	2	28	0	7	14	21	28	0	7	7
7071	٥	0	0	0	0	0	0	0	0	٥	0	0	0	0
7072	٥	0	٥	0	•	•	٥	٥	0	<u>-</u>	٥	0	0	•
7073	Ŷ	0	0	0	0	0	0	0	0	•	0	0	0	0
1/07	0	۰	٥	0	0	0	0	0	0	٥	•	0	0	0
7075	0	0	0	0	0	0	•	0	0	0	•	0	0	0
7076	0	0	0	٥	0	0	0	0	0	0	0	۰	0	0
7077	٥	٥	٥	٥	•	•	٥	٥	0	•	٥	٥	0	0
7078	٥	0	0	0	0	•	9	0	0	•	۰	٥	٥	0
7079	0	0	٥	٥	٥	•	0	٥	0	•	۰	۰	٥	0
7080	0	0	0	۰	0	0	a	٥	0	0	•	٥	٠	0

Individual Animal Detailed Clinical Observations

36						Det	ClinObs (Rem	DetClinObs (Removal from Cage)	ge)					
ekgday oup 4	Membranes	Mucous Menhanes	Salivulon	Marcus Salivation Salivation Salivation Salivation Salivation	Salivation	Salivation		Emaciation	iznacial (on	Ernciation	Emaciation	Emuciation	Emaciation Emercation Emacration Emacration Pitoerection Pilocrection	Pilocrection
	۲,	28	0	7	ı	77	87	0	6	Ξ	21	28	•	7
707	0	0	0	0	0	0		٥	0	0	0	٥	0	0
7072	٥	٥	0	•	0	0	•	•	0	٥	•	•	•	0
7073	c	٥	0	0	0	0	0	۰	0	0	0	•	•	0
7074	0	0	0	0	0	•	•	•	0	0	0	٠	•	0
2075	٥	0	0	0	0	c	0	0	c	0	0	0	0	0
7076	0	0	0	0	0	•	0	0	0	0	•	•	•	9
7077	٠	0	•	•	0	٥	0	•	0	٥	•	٥	•	•
8.07	٥	•	0	0	0	0	0	0	•	0	٥	0	0	0
7079	0	۰	0	٥	0	۰	0	•	۰	0	٥	0	0	0
7080	9	0	9	٥	0	٥	•	•	0	0	•	0	2	0

536						Det	ClinObs (Rec							
ng/kg/day Group 4	Pilocrection	Pilocrection	Pilocrection	Far/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Fur/Skin	Muscle Tone	Muscle Tone	Muscle Tone	Musele Tonc	Muscle Ton	Respirator Paltern
	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	Ð	0	0
7072	0	0	0	ø	0	0	0	0	U	Ų	Q	U	0	0
7073	0	0	0	Ð	0	0	0	0	0	0	0	0	- 8	0
7074	٥	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	υ	Ð	0
7076	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7077	0	0	0	0	0	0	0	Q.	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	j o	υ	0	0	0	0	0	0	0	0

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1536				DetClinObs	DetClinObs (Removal from Cage)	сот Саде)					Detclin	DetClinObs (Open Field Obs)	eld Obs)	
mg/kg/day Group 4	Respiratory Paltern	Respiratory Respiratory Pupillary Pattern Pattern Pattern Reflex	Respiratory Pattern	Respiratory		Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Pupillary Reflex	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal	Activity/ Arousal
	7	2	12	88	0	7	3	11	38	٥	_	7	21	28
7071	0	0	0	0	0	0	0	0	0	0	٥	٥	٥	-
7072	Ð	۰	0	۰	0	•	٥	0	-	0	>	-	0	Þ
7073	o	۰	0	0	0	٥	•	0	٠	0	٥	0	0	0
1.07.4	0	۰	0	•	0	•	•	•	•	0	۰	0	٥	0
7075	0	0	0	0	0	0	0		•	0	٠	0	o	0
7076	0	0	0	•	0	0	٥	•	•	0	۰	0	٥	0
707	0	٥	0	0	0	٥	۰	•	٠	0	٠	>	٥	0
30.02	0	٥	0	0	0	0	0	0	÷	0	•	•	٥	0
97.07	0	•	•	۰	0	٥	۰	0	٥	0	٥	•	۰	0
7080	0	0	0	٥	0	ə	÷	0	÷	0	3	0	٥	0

Individual Animal Detailed Cinical Observations

536						ď	et Clin Obs (O	DetClinObs (Open Field Obs)						
ng ng ng irosp 4	Convulsions	Contabinus Contubinus Centubinus Contubinus Tranon	Convulsions	Canubions	Convibions	Гистогу	Tremos	Transon	Tremore	Tremors	Posture	Posture	Posture	Posture
	s	7	#1	71	82	0	r-	7	21	28	o	7	11	21
1707	0	0	0	φ	٥	0	0	0	0	0	0	0	θ	0
7072	٥	0	0	٥	-	•	0	0	•	0	•	0	۰	-
7073	0	0	0	٥	0	•	0	0	٥	0	•	٥	0	•
7074	۰	0	0	0	•	0	0	۰	•	•	0	0	0	•
7075	¢	0	0	a	0	•	0	0	•	0	•	0	0	•
7076	•	0	0	0	٥	•	0	0	•	•	۰	0	0	•
7.077	٠	٥	٥	•	•	۰	٥	0	•	٥		٥	0	\$
7078	٥	0	0	0	0	0	0	0	0	•	0	٥	0	5
7079	0	٥	0	٥	•	٥	0	0	٥	•	٥	0	•	9
0000	٠	<	٠	_		·	•	٠	٠,	ς	=	æ	-	<u>-</u>

Individual Animal Detailed Clinical Observations

536							DetClinObs (Open Field Obs)	pen Field Ob	۰					
nipkaday Grap 1	Posture	Gait	Ja5	jā Čē	Cart	Gait	Locomotion Locomotion Locomotion Locomotion Locomotion Defecation Defectation	Locomolon	Locomotion	Locomotion	Locomotion	Defection	Defecation	Deferation
	28	0	7	≟	21	28	0	7	±	ឌ	82	0	7	Ξ
7071	0	0	0	Ω	0	٥	٥		0	0	٥	o	٥	0
7072	٥	٥	٥	~	0	0	٥	0	۰	0	٥	9	>	9
7073	0	0	0	0	0	0	۰	0	0	0	٥	0	۵	0
7074	0	0	•	•	0	٥	۰	•	۰	0	٥	0	0	c
\$707	0	φ	0	0	0	0	٥	0	0	0	٥	0	0	0
7076	0	φ	0	۰	Q	0	•	0	0	0	0	0	•	0
707	٥	0	0	0	¢	0	٥	•	0	٥	0	0	٠	0
8:02	0	0	0	o	٥	0	0	0	0	0	0	•	0	0
6101	٥	0	0	0	۰	0	٥	•	٥	Þ	0	•	0	0
7080	0	0	0	=	Ç	_	4	_	c	4	-	4	-	=

320

1536						Ţ	aclinObs (C	pen Field Ob	5)					
mg/kg/day Group 4	Deferation	Defecation	Urination	Urination	Urination	Uringlion	Urination	Umusual Behaviors	Umusual Behaviors	Unusual Behaviors	Unusual Behaviors	Unusual Behaviors	Vocalization (OF)	Vocalization (OF)
	31	28	ō	7	14	21	28	0	7	14	21	28	0	7
7071	0	0	0	0	0	0	0	0	0	0	Ð	θ	0	0
7072	0	0	0	0	0	0	0	0	0	0	v	Q	0	U
7073	0	0	0	0	0	0	0	0	0	0	0	Ü	0	0
7074	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7075	0	0	0	0	0	0	1)	9	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	Ð	U	0
7078	0	0	0	0	0	0	0	0	0	U	0	0	0	0
7079	0	0	0	0	0	0	0	0	0	0	0	0	v	0
7080	0	0	0	0	D	0	0	0	0	0	l 0	υ	0	0

PSL Study Number 43166 A 28-Day Dietary Study in Rats

		$\overline{}$										
(Sar) bla	Voculizato (CD)	38	0	0	0	0	0	0	•	•	0	0
Det ClinObs (Open Freid Obs)	Grafization Vocalization (OF) (OF) (OF)	21	0	٥	0	٥	٥	0	٥	0	٥	٥
Detcain	Voralization (OP)	=	0	٥	0	0	0	0	٥	٥	•	•
1536	nigkiguday Group 4		107	2707	5,073	7074	27.07	7076	7077	87.07	9707	7080

APPENDIX I: INDIVIDUAL ANIMAL BODY WEIGHTS1

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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 I	Day(s) Relative to Start Date				
	0	7	1.4	21	28
7001	240	297	345	396	429
7002	232	273	327	362	382
7003	238	288	334	379	401
700·I	234	271	310	343	360
7005	228	267	305	340	357
7006	247	303	347	104	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
\$D	6.1	14.0	16.5	22.7	28.8
N	10	10	10	10	10

Sex: Male Bodyweight ((g.)
------------------------	------

512 mg/kg/day Group 2			Day(s) Rela to Start Da		
	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
7 0 25	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

1024 mg/kg/day Group 3		1	Day(s) Rela to Start Da		
•	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
7017	239	304	360	106	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		<u> </u>	Day(s) Relative to Start Date	ive le	
Group 4	0	4	14	21	28
7061	241	295	342	380	404
7062	234	288	335	374	403
7063	233	270	305	345	369
7061	3:10	춫	363	- 48	÷
2002	546	308	362	5	432
2006	239	2	351	38	Ş
7067	24.1	306	355	36	420
7068	226	381	326	362	385
6902	229	293	326	360	379
7070	231	284	330	366	396
Mean	236.3	292.8	339.5	379.9	405.5
CS	6.7	12.2	18.6	32.7	24.1
×	10	9	2	2	2

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g) Day(s) Relative to Start Date mg/kg/day Group I 7012 יו 220 Mean 174.1 198.3 218.8 239.2 249.8 SD N 12.3 14.8 21.9 21.0 24.0

^{1 [}RC:Reweighed, food and water OK]

PSL Study Number 43166 A 28-Day Dietary Study in Rate

Sex: Female Bodyweight (g)

512 mg/kg/day Group 2			Day(s) Relat to Start Da		·
	0	7	14	21	.28
7031	192	217	239	246	257
7032	175	195	208	224	237
7033	173	200	210	22811	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 12	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

1024 mg/kg/day Group 3			Day(s) Rela to Start Da		
	0	7	14	21	28
7051	162	189	202	210	229
7052	162	192	216	224	238
7053	182	210	231	249	267
705-1	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

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Fernale Bodyweight (g)

1536		α -	Jay(s) Reintive to Start Dete	₹.		
igo Ago umy inomp 4		_	and the contract of			
	0	7	=	21	28	
1.07.1	171	198	212	2:10	248	
7072	168	*	218	23	246	
7073	181	208	232	3	263	
707-4	179	195	215	526	23.4	
7075	177	201	218	23	24.1	
2076	163	86	219	묽	245	
7007	187	215	241	360	27.1	
7078	162	161	213	774	237	
6/0/	961	215	246	258	262	
7080	159	184	661	225	240	
Mean	174.3	199.3	221.3	238.0	248.7	
SD	11.9	10.5	14,3	13.1	12.4	
Z	01	2	2	01	10	

APPENDIX J: INDIVIDUAL ANIMAL MEAN DAILY BODY WEIGHT GAIN¹

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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		ē.	Day(s) Relative to Start Date	a,	
	0 → 7	<u></u>	7 → 14 14 → 21 21 → 28	21 → 28	0 28
7001	8.1	6.9	7.3	4.7	8.9
7002	5.9	7.7	5.0	5.9	5.4
7003	7.1	9.9	6.4	≍	5.8
7007	5.3	5.6	4.7	-;	÷.5
7007	9.6	5.4	5.0	2.4	4.6
7006	8.0	63	8.1	<u></u>	6.7
7007	9,4	7.1	0.9	£	6.7
7008	7.6	6.4	4. L.	3.6	5.3
4000	8.0	6.4	9.6	2.7	5.7
7010	8.3	5.3	5.6	1.3	5.1
Mean	7.33	6.37	5.84	3.07	59:5
as	1.35	0.77	1.15	1.06	0.84
z	2	2	2	2	10

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			ny(s) Relati to Start Date		
	0 → 7	7 -+ 14	1-1 → 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
SĐ	0.94	1.30	0.75	0.91	0,83
N	10	10	10	10	10

Individual Arimal 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		Ğ -	Day(s) Relative to Start Date	e	
	0 → 7	7 + 14	14 21	21 28	028
7041	6.1	7.4	6.3	3.6	6.6
7042	8.0	8.7	च •	=	7.1
7043	7.1	5.7	6.3	2.3	5.4
7047	9.1	8.3	6.9		7.3
7045	7.9	7.0	5.9	33	6.0
7046	9.1	9.0	6.3	4.7	7.3
7047	9.3	8.0	9'9	3.9	6.9
7048	8.9	8.1	7.3	6,4	7.3
7049	5.4	5.6	4.0	3,9	7.7
7050	6.4	4.6	4.4	17	4.2
Mean	7,74	7.24	6.13	3.67	6.20
SD	1.40	(ફ-1	1.12	1.10	1.14
z	으	2	2	2	9

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166 A 28-Day Dietary Study in Rats

<u>a</u>	can Dauly B	ody Wenglit	Mean Daily Body Weight Gam (g/day)	ا	
1536 mg/kg/day Group 4		a	Day(s) Relative to Start Date	a 41	
	07	7	14 21	21 1 28	0 → 28
7061	7.7	6.7	5.4	3.4	5.8
7062	7.7	6.7	5,6	Ţ	6,0
7063	5,3	5.0	5.7	3,4	5°7
7064	9,1	-8	7.9	0.4	₹.
7065	6.8	7.7	6.0	4.0	9.9
7066	9.8	7.4	6.4	3,6	6.5
7907	8,9	7,0	5.6	3,7	63
7068	7.9	6.4	5.1	3.3	5.7
7069	9.1	4.7	6.5	2.7	5.4
7070	7.6	9'9	5.1	4,3	5.9
Mean	8.07	6.67	5.77	3.66	6.04
SD	91.T	1.13	98.0	0.47	0.70
7	2	_	2	_	2

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			ay(s) Relati 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

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Fentale Mean Daily Body Weight Gain (g/day)

512 mg/kg/day Group 2			ay(s) Relati 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

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			uy(s) Relati 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

1536 mg/kg/day Group 4			my(s) Relati 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 CONSUMPTION1

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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.

PSL Study Number 43166 A 28-Day Dietary Study in Rate

Sex: Male Mean Daily Food Consumption (g/day)

0 mg/kg/day Group 1			, , ,		Relative at 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. t	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

512 mg/kg/day Group 2					Relative nt 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

PSL Study Number 43166 A 28-Day Dietary Study in Rate

Sex: Male Mean Daily Food Consumption (g/day)

1024 mg/kg/day Group 3					Relative nt Date			
Опосро	3 → 7	7 → 10	10 14	14 17	17 → 21	21 24	24 2B	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.B	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

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					Relative nt 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

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (glday)

0 mg/kg/day Group 1					Relative rt 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

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					Relative nt 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

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 10 → 14 | 14 → 17 | 17 → 21 21 -- 24 | 24 --- 28 | 3 -- 28 7 → 10 7051 18.4 15.8 20.5 18.4 20.9 17.5 17.7 17.3 7052 20.9 17.5 18.4 17.7 17.3 15.8 20.5 18.4 7053 15.5 22.3 20.3 22.0 19.7 20.6 19.5 20.8 7054 15.5 22.3 22.0 19.7 20.6 19.5 20.8 20.3 7055 16.3 21.4 20.8 22.9 23.2 20.4 20.0 20.6 7056 22.9 23.2 20,4 20,0 16.3 21.4 20.8 20.6 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 15.97 Mean 21.05 19.30 19.45 18.47 19.35 21.08 19.40 SD N 0.34 1.31 2.26 1.12 1.22 1.52 0.91 1.09 10 10 10 10 10 10 10 10

PSL Study Number 43166 A 28-Day Dietary Study in Rate

Sex: Female Mean Daily Food Consumption (g/day)

1536 mg/kg/day Group 4					Relative nt Date			
Group 4	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 = <u>Mean Daily Body Weight Gain</u> Mean Daily Food Consumption

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.

0 mg/kg/day Group I			Relative rt 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		to Star	to Start Date	
•	0 - 7	7 1 1	<u>12</u> → 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	01.0
7025	0.32	0.21	0.21	0.10
7026	0,33	0.30	0.20	0.12
7207	0.30	0.21	0.25	0.13
7028	0.27	0.20	81.0	9.08
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
CIS	0.038	0.043	0.022	0.032
Z.	10	01	10	10

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

1024 mg/kg/day Group 3			Relative rt Date	
,	0 → 7	7 14	1/1 → 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	0.010
N	10	10	10	10

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

1536 mg/kg/dny Group 4			Relative rt 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

0 mg/kg/day Group I			Relative rt Date	
	0 7	7	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

512 mg/kg/day Group 2			Relative rt Date	
21114	07	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
703-1	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	10,0-	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

	Food Efficiency	
Ì	Sex: Female	

1024 mg/kg/day Group 3		Day(s) to Star	Day(s) Relative to Start Date	
•	7-0	7 1	14 - 21	21 28
7051	0.23	0.10	70'0	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	60.0
7055	61.0	90.08	0.22	0.07
7056	0.28	0.17	0.13	0.07
7057	91.0	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	90.0	0.14
Mean	0.226	0,146	0.112	0.109
as	0.037	0.033	0.049	0.033
z	10	10	2	01

Sex: Female	Food Effici	енсу		
1536			Relative	
mg/kg/day		to Sta	rt Date	
Group 4			T	
	0 → 7	7 → 14	14 21	21 → 28
	L			
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	0.014
N	10	10	10	10

APPENDIX M: INDIVIDUAL ANIMAL MEAN DAILY DIETARY INTAKE OF SOY LEGHEMOGLOBIN PREPARATION¹

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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

•

		ofter (day)			
Sex: Male Die	Dietary Intake Variable (mg/kg/day)	e ng ang j			
0 mg/kg/day Group 1			Day(s) Relative to Start Date		
	7 0	7 14	14 21	21 28	028
1001	0	Û	0	0	0
7002	•	0	0	0	0
7003	0	0	0	0	0
1007	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
CS	0'0	0.0	0.0	0.0	0.0
z	10	2	9	91	01

Individual Animal Mean Dietary Intake.

PSL Study Number 43168 A 28-Day Dietary Study in Rats

512 ng/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 Dielary Intake.

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

1024 mg/kg/dny Group 3			Day(s) Relative to Start Date		
C.O.A.F.S	0 7	7 ~-> 14	1421	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 43168 A 28-Day Dietary Study in Rats

Dietary Intake Variable (mg/kg/day)		
etary Intake V		
sex: Male Die		
š	I	

1536 ng/kg/day Prong 4			Day(s) Relative to Smrt Date		
	70	7 14	14 21	21 28	0 28
7061	1338	1587	1.463	1411	1373
7062	1374	1623	1489	1424	1397
7063	1435	1745	1669	1576	1516
-502	1327	1504	1389	1303	1302
7065	1421	1569	1458	1417	1388
7066	1463	1617	1496	1450	1425
7007	1529	1631	1488	1471	1449
2002	6591	1776	1620	1603	1576
7069	9151	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	81.18	92.5	78.6
z	01	10	01	92	01

Individual Animal Mean Dietary Intake

PSL, Study Number 43166 A 28-Day Dietary Study in Rats

		0 28	0	٥	0	0	0	0	0	0	0	0	0.0	0.0	01
		21 28	0	٥	•	0	0	0	0	0	0	0	0.0	0.0	91
	Day(s) Relative to Start Date	14-+21	0	٥	0	¢		0	0	0	0	0	0:0	0.0	01
ng/kg/day)		714	0	0	0	0	0	0	0	0	0	0	0.0	0.0	10
Dietary Intake Variable (mg/kg/day)		2 0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	10
Sex: Fenale D	0 mg/kg/day Group 1		102	7012	7013	7014	7015	7016	7017	7018	2019	7020	Mean	CS	z

Individual Animal Mean Dietary Intake.

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day) mg/kg/day Group 2 Day(s) Relative to Start Date 0--7 7 --- 14 14 --> 21 0 --- 28 21 ~ 28 497.8 Mean 498.0 541.9 518.8 182.1 SD 53.9 42.8 43.5 49.9 41.9

Individual Animal Mean Dietary Intake.

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Sex: Female L	Sex: Female Dietary Intoke Variable (mg/kg/day)	mg/kg/day)			
1024 mg/kg/day Grans 3			Day(s) Relative to Start Date		
	6 7	7 14	14-+21	21 28	0 28
1902	1013	1082	1046	1087	1022
7052	100:1	1037	980	1033	982
7053	1003	1077	1041	896	986
7054	971	1044	1012	756	963
7055	957	1102	666	016	956
7056	1035	1119	1015	816	866
7057	1001	1066	1018	1018	886
7058	096	1004	7.1.6	1003	956
7059	975	1014	979	556	948
2060	1038	1104	1083	1961	1035
Mean	6.566	1064,6	1015.1	0,1466	983.4
CS	29.2	39.2	34.3	26.0	29.0
z	10	10	9	10	01

Individual Animal Mean Dietary Intake.

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Day(s) Relative to Start Date mg/kg/day Group 4 7 -- 14 14 --> 21 0 --- 28 0---7 21 -- 28 1537.2 1460.2 1470.4

92.3

79.0

88.2

1604.6

116.7

Dietary Intake Variable (mg/kg/day)

1481.1

115.0

Mean

SD

N

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.l. 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.Š.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.

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 Ro	ported to:	110
Audit Dates	Principal Investigator (PI)	PI Manugement	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

	C	ERTIFICATION		
the undersigned, declar		Triangle Man and	data obtained f	rom this study.
	(b) (6)		And A storage (and date wheely
Issued by Principal Investigator:	() ()			20 July 201
r riberpar investigator.	Denise I	lohan, B.A., MLT (ASC	Pi	Date
	Senior Staff Tox	icologist & Pathology C	oordinator	

-4-

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
hemoglobin
hematocrit
mean corpuscular (cell) volume
mean corpuscular (cell) hemoglobin
mean corpuscular (cell) hemoglobin concentration

red cell distribution width absolute reticulocyte count platelet count white blood cell count differential white blood cell count

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 alanine aminotransferase

glucose total protein Clinical Pathology Results for

Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

sorbitol dehydrogenase albumin alkaline phosphatase globulin total bilirubin calcium

urea nitrogen inorganic phosphorus

creatinine sodium cholesterol potassium triglycerides chloride

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 Sta	atistical 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

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- Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics* 20, 482-491.

TABLES

Clinical Pathology Results for

Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

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
                     red blood cell count
hemoglobin
         RBC
```

- nemoglobin
HCT - hematocrit
MCV - mean corpuscular (cell) volume
MCH - mean corpuscular (cell) hemoglobin
HCHC - mean corpuscular (cell) hemoglobin concentration
KDW - red cell distribution width нене RDW PLT red cell distribution width platelet count platelet count
white blood cell count
absolute neutrophil (all forms)
absolute lymphocyte
absolute monocyte MRC VNEA ALYM MON

- absolute monocyte
- absolute monocyte
- absolute esinophil
- absolute basophil
- absolute large unstained cell
- absolute reticulocyte AEOS ABAS ALUC ARET

Summary of Coagulation Values

PT - prothrombin time
APTT - activated partial thromboplastin time

Summary of Clinical Chemistry Values

AST ALT aspartate aminotransferase alanine aminotransferase SDH porbitol dehydrogenase ALKP alkaline phosphatase total bilisabin BILI urea nitrogen CREA creatinine CHOL cholesterol TRIG GLUC triglycerides glucose total protein TP albumin GLOB globulin CALC calcium inorganic phosphorous sodium potassium chloride MA K CL

Summary of Urinalysis Values UVOL - volume

orinalysis

OOL - volume

pil - the '
SG -
TRO the logarithm of the reciprocal of the hydrogen ion concentration opecitic gravity URO urobilinogen protein

TABLES

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

MOTES:

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:

SDiff - ((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 tounding.

Table 1 Summary of Hematology Values for Male Rats

Sex Male	Day(2) Raistwa to S	Start (Nata	0 mghgiday Circup t	512 mg/kg/day Group 2	ცისი 3 იაგმეგის 1854	1536 mg/kg/day Group 4
RBC	22	Voan	7 72	7.60	7.61	7.70
(x10°6\£.)		SO	0.23	034	0.35	0.27
j		н	10	10	10	10
		%04		-15	.15	-93
HG8	22	Mean	15,6	15.4	15.5	15.9
(g/dL)		SD	0.3	0.6	ÜĠ	8.4
		N	10	10	10	10
		የውሰ		-1,5	-1 Q	1.4
HCT	22	NeW	43.5	45.1	45 t	45.9
(56		SD	0.9	1.5	17	ΩĐ
[14	10	10	19	10
		804		-0.0	-0.8	10
WEV	17	User	54 b	593	5P.3	5P 7
(EL)		SD	10	2.3	15	1.9
		16	tG	\$0	10	tō
		NOW.		07	0.7	13
MCH	22	Non	20.3	29.3	20 4	20.6
(P\$)		50	0.5	0.9	05	97
l		N	10	10	10	tΩ
		%0#		0.2	ÛĠ	10
MCHC	22	Maun	34.4	34.2	344	34.5
(gfdL)		50	0.4	0.4	03	0.5
		N	10	10	‡D	10
		94D#f		-0.5	-01	0.4
ROW	22	Mean	12.1	125	125	12.3
(%)		SD	0.3	0.5	0.3	0.5
ŀ		н	10	10	10	ŧĐ
		MD#		3.0	33	1.6
PLT	22	Moore	1160	1202	1171	1227
(x10^3\&.)		SD	121	59	76	185
		N I	10	10	10	tĐ
ŀ		ND#		36	10	5.8

General Footnote: [Statistical Test: Azove and Dunnetl'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)

ex Male			0 mg/kg/day Group 1	512 mg/ig/day Group 2	1024 mphyldsy Group 3	1536 mg/kg/day Group 4
	Dayle) Relative to S	int Date	,			-
WEC	22	Mean	13.00	1441	11.13	13 45
(#10°Oyst)		50	1 33	267	1.62	441
		N	30	10	10	10
		SECNET		10.8	-14.4	34
ANEU	77	Mano	1.01	1.99	1.75	1,57
(x10°3\u6.)		50	0.87	0.43	0.41	0.63
		N	10	10	14	10
		1604		41	-8.1	-17.8
AL YM	72	Mean	10.49	11 79	1 1.05	11 29
(10°3ነμέ.)		50	1.17	2.48	1.70	4 15
		N	10	10	10	10
		WD#		124	-15.5	77
AMON	27	Mean	031	0.34	9.78	6 30
(c10*3\uE)		50	0.10	0 11	0.05	© 10
ı		N	10	10	10	16
1		知識		10.2	-9.8	.13
AEOS	22	Mean	0 12	ê 13	0.11	0 11
(e10*34d.)		so	0.04	9.68	0.04	0.05
		N	\$0	10	10	10
		904		44	-1.2	-74
ABAS	77	Mass	₽ û \$	0 09	0.07	Q 10
(+10*3hit)		50	0.03	004	0.02	0 06
		N	\$ 0	10	10	10
		180#		-50	-27.0	0.2
ALUC	22	Mean	0.08	0.08	9,08	0.98
(x10*3/pL)		so	0.03	0.03	0.02	0.04
		N	10	10	13	10
		560M		-81	-27. 0	-24
ARET	22	Mean	232.6	235.8	245.3	243 8
(±10°3\st.)		80	31.2	40.7	24.1	41.1
		N	10	10	10	10
j		59047		1.4	5.9	48

General Footnote: [Statistical Test: Anove and Dunnett's test Transformation: Automobil)

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

iax Fortule	Dayls) Relative to	Start Clate	0 mg/kg/day Group 1	512 mg/10/day Group 2	1024 mg/lg/sky Geoup J	1538 mg/kg/day Group 4
ABC T	22	Mean	7.59	801 •	7.86	763
(infordsult)	-	90	0.24	0.18	0.24	0.30
		N	3 D	10	10	10
		5604		54	36	Q.e
HGB	27	Mean	153	10.2 •	15.7	15.5
(g/di.)		80	0.5	03	0.4	46
		N	10	10	10	10
		56341		57	2.5	0.9
HCT	72	Mean	43.0	45.9	417	440
(%)		SO SO	12	12	1,3	17
		N	30	10	10	10
		56041		52	24	0.9
MCY	77	Mean	57.5	57.4	56 B	57.7
(FL)		so	11	22	1.2	27
1		N	to	10	10	10
		MONT		-0.2	-1 f	0.4
U CH	22	Mean	20.2	20.2	20.0	20 3
irgi		30	0.3	0.7	0.5	07
		N	Ot	10	ig	10
		1404		01	-10	03
MCHC	22	Mean	35.2	35 3	35,2	35 ?
(9 '4 L)		50	07	83	0.4	05
		N	10	10	15	10
		1604		03	01	0.0
RO#	22	Mean	11.3	113	†1.2	115
(34)		30	0.4	05	0.3	85
		N	10	10	10	10
		1000		81	-0.4	1.7
PLT	22	Mean	f 198	1176	1239	1229
(±16*34µL)	•	80	108	127	115	114
		N	70	10	16	10
		1:20WF		-11	34	33

General Footnobe, [Stafstbool Test, Anovo and Dunnett's test Transformation Automobil 1 p=. Test Dunnett 2 Sided p < 0.05]

Group 2, 512 mg/kg/day of fest substance corresponds to 250 mg/kg/day of the active ingredient. Group 3, 1024 mg/kg/day of fest substance corresponds to 500 mg/kg/day of the active ingredient. Group 4, 1536 mg/kg/day of fest substance corresponds to 500 mg/kg/day of the active ingredient.

Table 2 Summary of Hematology Values for Female Rats (Continued)

kir Fernale			o mghaiday Grave I	512 rng/kg/day Group 2	1024 mg/to/day Group 3	1538 mg/kg/day Group 4
	Dayls) Relative to St.	act Date				,
WBC .	22	Mega	10.08	11 67	11.59	10 19
(±10°35±L)		so	1 70	1 75	3.35	3 72
		N	10	10	10	10
		5004		177	15.0	t 1
ANEU	22	Mean	1 48	1.58	1.6 1	1 54
(x10°3/uE)		SO.	0.30	0.58	0.85	<u>!</u> 10
		N	t0	10	10	10
		*606		53	13.9	40
AL YM	72	Mean	8 15	9.74	9,29	871
(±10°3/uL)		80	1,58	_143	2.31	2 88
		N	19	10 :	10	19
		94047		195	14.0	9.7
AMON	77	Man	0.25	9 79	0 33	N 22
(x10°3\u£)		50	0.15	966	0.15	0 14
		N	10	10	10	to
		NO#		167	32.5	411
AEOS	22	Mean	B 11	0 13 :	0.15	0 12
(x10°35,1L)		SO	0.03	904	0.05	0.90
		N	10	10	10	10
		14C2AF		214	35.8	10
ABAS	22	Mean	0.04	007 **	0.05	1 05
(±19°3\nL)		90	0.01	0.03	0.03	0.04
		N	10	10	10	10
		1604		93.2	64.1	46 ?
ALUG	22	Mean	0.05	0 07	0.07	0.65
(*10,3A7)		30	0.02	0 02	6.03	0.04
		N	†Đ	10	10	10
		1404		29.1	24.2	29
ARET	22	Mean	205.0	182.4	163.1	184.2
(x10°3\sul.)		30	33.9	32.9	30.0	33.7
į		N	\$ 0	10 .	10	10
		%D#F		-113	-17,8	-10 \$

General Footnote (Statistical Test Anova and Dunnet's last Transformation Automotic) I [#- Test Dunnett 2 Sided p<0.95]

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 tost substance corresponds to 750 mg/kg/day of the active ingredient.

Table 3 Summary of Coagulation Values for Male Rats

Sex Male			0 mg/tg/day Group t	512 mg/kg/day Group 2	1024 mg/kg/day Group J	1535 mg/kg/day Group 4
	Oregia) Relative to	START DATE				
PT	29	Visari	10.7	10.7	10.6	10.8
(sec)		so	0.3	0.4	0.2	0.2
		N.	10	10	10	10
APTT	29	Mean	20.2	23 8	24.9 6'	23.9 %
(sec)		80	24	5.3	89	4.8
		N	10	10	10	19

General Footnote (Statistical Test: Anova and Dusnetts test Transformation Automatic) 1 [Q - Test: Dunnett Noo-Parametric 2 Sided p < 0.85]

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

Table 4 Summary of Coagulation Values for Female Rats

Cary(s) Relative to Start Date		0 m phgiday Group 1	512 mg/kydsy Group 2	1024 mg/kg/day Group J	1936 mgAgiday Group 4	
PT	30	Mean	10.0	0.8	10.0	9.8
(*60)		80	0.2	0.2	0.3	0.2
		N	10	10	18	19
APTT	30	Mean	21.9	20.0	20.8	19.4
(96C)		SO	25	31	50	1,0
		N	10	10	10	10

General Footnote (Statistical Yest, Angel and OurnetTs last Transformation Automatic)

Group 2 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingrediem. Group 3, 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingrediem. 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

er, Mele			0 m arkg/dar / Group 1	512 mg/kg/day Group 2	1024 mpkg/day Group 1	1936 mg/kg/day Group 4
	Cop(s) Relative to St	art Date			2.24	
AST	72	Vear	73	76	79	78
(UAL)		SO SO	8	8	7	8
		l N	5	ġ.	ō	8
		140#		40	7.5	9.9
ALT.	22	Mean	29	28	28	30
(UA)		so s	4	4	3	4
		l N	10	10	10	10
		140#		-3 1	-24	24
SD∺	72	Ven	6.2	6 1	84	80
(nt)		50	1.4	17	24	14
			5	9	8	8
		ND#		-0.8	27	.19
¥ΓΚĐ	22	Mean	183	216	216	205
(UAL)		80	24	29	44	42
		N N	10	10	10	10
		%D#		18-6	18.5	12.3
8171	72	Mean	0.17	0 17	0 18	0 18
(mg/dL)	ĺ	so	0.02	0 02	0.02	0.92
		N N	10	10	10	10
		740 m		12	41	5.9
SUN	77	Mean	10	11	10	13
(mg/dt.)		so	1	1	1	2
		N N	10	10	10	10
		140/1		4.8	-3.8	1.0
CREA	22	Mean	0.22	0.23	0.23	0.21
(mg/dt.)		so	0.01	0.02	0.02	0.02
		N N	10	10	10	10
		NOW		36	4 5	-59
CHOL	22	Меал	76	73	72	57
(mg/dt.)		so	16	27	14	12
		N N	to	18	10	10
		100		-34	-54	-117

General Footpote (Statistical Test: Annya and Durnet's test Transformation: Automatic)

Group 2, 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the servicing redient

Group 3, 1023 mg/kg/day of lest substance corresponds to 500 mg/kg/day of the active arguedient. Group 4, 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active arguedient.

Table 5 Summary of Clinical Chemistry Values for Male Rats (Continued)

ax Male			ngilgisay Group t	512 mg/kg/day Group 2	1024 mg/kg/day Group J	1535 កាព្យក់ដូវ៤៩y Group 4
	Cay(s) Relative to 5	itart Date				
TRIG	22	Mean	(d)	67	67 .	fêt
(mg/dL)		so	17	13	17	28
		N	to	10	10	10
		MD#		1. 0	0.9	2.4
GLUC	22	Mean	95	100	102	98
(mg/dil.)		50	12	9	13	8
		N	10	10	10	10
		NOA		5.4	71	2.5
₹₽	22	Mean	6.0	6.1	62	60
(p\dL)		80	0.2	0.2	0.2	Q.2
		N	10	10	10	to
		ND#	i	۵7	28	0.2
ALB	22	Waan	3.1	32	33 •.	3.2
(P (4)		SO S	0.1	0.1	01	0.1
		N	10	10	10 .	10
		%DHT		22	41	19
GE08	22	Mean	2.9	28	29	2.8
(g/dL)		\$0	0.1	0.2	0.1	0.2
		N	10	10	10	10
	,	14017		-1.0	14	-1,7
CALC	22	Moon	10.4	10.4	10.4	10.5
(mg/dL)		80	0.2	0.2	0.2	0.2
		N N	10	10	10	10
	1	NO#		-0 1	01	0.8
PHS	22	Mean	8.0	6.7	8.0	8.5
(m g/dl.)		50	0.4	0.4	0.9	0.4
		n	5	9	0	8
	l	*401	<u> </u>	9.6	21	-0.3
34	22	Mean	149.5	142.1	141 3	141.7
gremoit.)		50	4.2	06	07	8.9
		N	10	10	10	10
		1900		11	04	6.0

General Footnote: [Statistical Feet: Anover and DurnetTe Less Transformation: Automatic]

1 |#- Test Ownett 2 Sided p < 0.05]

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

Table 5 Summary of Clinical Chemistry Values for Male Rats (Continued)

Sax Malo	Chay(s) Relative to Start Date		B mgAgi day Group 1	512 sng/kg/day Group 2	1024 mgh.g/day Gloup 3	1535 rng/kg/day Group 4
K (penolit.)	22	1 1	5.03	5 19	5.55 •	5.10
district.		SO SO	0.25	G 26	180	0.25
		l N	t0	10	10	10
		*4DAT		31	104	1.4
CL	22	Wear	100.8	1020	101.6	\$01.7
(mmail)		50	2.4	1.0	0.9	1.2
		N N	10	10	19	të
		NO#		12	6.8	0.9

General Footnote: [Statistical Test, Argun and OurnetFaltest Transformation Automatic] I [8- Test Ourneti 2 Sided p < 0.05]

Group 2: 512 mg/kg/May 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 3: 1024 mg/kg/day of test substance corresponds to 730 mg/kg/day of the active ingredient

Table 6 Summary of Clinical Chemistry Values for Female Rats

Sex Fernsie			ij mg/lg/day Group f	512 mphydday Group 2	1024 mg/kg/day Group 3	1535 my/kg/day Group 4
	Clay(s) Relative to S	tart Date	7- 7-1			
AST	22	West	69	69	64	65
(UL)		80	6	10	8	6
		N	9	9	10	10
		NO.	-	.03	-7.4	-6.5
ALT	22	Mean	25	28	25	27
(VA)		50	4	5	8	5
		N	16	10	10	10
		%D#I		. 28	-0.4	5.2
SDH	22	Weam	8.7	81	BQ	9.9
(7A7)		so so	2.2	12	0.9	2.5
		N	9	9	10	to
		*D#		-7.4	-90	12.9
ALKP	22	Мовт	137	107	121	108 **
(UNL)		80	ta	19	29	25
		N	10	10	10	to
		%D#		-22.4	-12 1	-21.3
EH1	22	Mayer	0,1\$	0 19	0.20	0.19
(mg/dL)		80	0.82	002	0.02	0.03
		N	10	10	10	30
		904		8.4	18.6	7.8
BLIN	22	Moon	12	11	12	12
(mg/dL)		so	2	1	2	1
		N	10	10	10	10
		%O #		-115	-0.8	0.0
CREA	22	Viezn	0.28	0.28	0.27	0.29
(mg\ժi)		so	0.02	0 02	0.03	0.83
		R	10	10	\$Đ	10
		%D#7		-69	-29	1.1
CHOL	72	Mean	85	95	98	94
(mg/dL)		50	11	10	19	22
		H	10	10	1 D	10
		*Dff		12.2	15.5	11.7

General Footnote, (Statistical Test, Anover and Durnett's test Transformation (Automatis) 1 (#- Test Dunnett 2 Sided p < 0.05)

Group 2, 512 mg/kg/day of test stabilistic 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 transdient Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active transdient

Table 6 Summary of Clinical Chemistry Values for Female Rats (Continued)

Sax Female			Q mg/kg/day Group 1	512 mg/kg/day Group 2	1024 mg/kg/day Grosp 3	1535 mg/kg/day Group 4
	Doy(e) Relative to Si	est Daine		-		
TRIG	22	Wear	37	: 38	48	72
(mg/dL)		80	6	9	15	e
		N N	to	10	19	10
		100		35	24 9	-4.3
GLUC	72	Mesn	118	103 ·	104 *	110
(ingidL)		80	15	10	10	14
		N N	10	10	18	10
		MON		-13.3	-120	-8.7
TP	22	Wean	6.4	67	68	67
(g\dL)		so]	0.3	0.4	0.3	0.4
		N	10	10	10	10
		%D#		51	56	3.7
ALB	22	Mean	3.5	37	37	3.5
(g\st.)		so	0.2	02	0.2	6.3
		N	10	10	10	10
		NO#		40	46	3.4
GL08	22	Wear	2,9	31	31 **	3.0
(g/dL)		so	0.1	0.2	02	Q.†
		N N	10	1B	10	10
	,	307		6.6	69	4.1
CALC	22	Mean	10.5	109 •	11.0 •	10.7
(ingrál)		so	0.3	0.3	0.3	0.4
		N	10	\$ D	10	10
		NO#T		38	51	18
₽HS	22	Mean	7.1	78	76	7.1
(mg/dt.)		so	0.5	` D6	0.4	Q.B
		N N	9	9	10	te
		140(1		9.7	85	-0.5
NA	22	Mean	149.3	140 6	t40 3	140.2
(mmol/L)		SO	1,1	06	0.7	1.1
		N	10	10	10	10
		NOM		02	a c	0.0

General Footnote (Statistical Test: Arrara and DurnetTe test Transformation Automatic) 1 |#- Test: Consist 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 5, 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient Group 4, 1436 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)

Sax Fernale	Over(s) Relative to St	ant Date	Greup !	512 mg/kg/day Group 2	1024 mghgday Grosp J	1536 mgApiday Group 4
к	22	Mean	4,5\$	463	4.72	4 74
grenski.}		80	0.33	0.38	D.21	0.38
		N N	t0	10	10	10
		ND#		1.5	35	4.0
CF	22	Meen	102.8	101.3 💌	101 1 💌	102.1
(mmatt.)		50	1,2	14	1.0	1,1
		N	10	10	10	10
		TKO#		-1.3	-1.5	0.5

General Footnote, [Stafatical Test, Aravir and Durnet's test Transformation Actomatic] I [a- Fart Quinett 2 Sided p < 0.05]

Group 2, 512 ng/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			ð mg%g/day Group 1	512 mg/sg/day Group 2	1024 mg/tg/day : Group 3	1536 mg/kg/day Group 4
	Dayls) Relative to Sta	est Date			i	
UYOL	22	Mean	11.7	11.5	12.3	14.3
(mL)		SO S	8 2	98	rз	1.7
		N	10	10	10	10
		500#		-18	48	27.0
pH	27	Mean	65	65	5.0	6,6
		SC SC	0.3	Ç.4	0.4	0.4
		N	10	ş	10	10
		160#		9.8	0.8	1.5
sa	n	Mean	1 027	1.027	1 026	1 D24
		SO SO	0.019	Q 015	0.015	0,019
		N	10	9	10	10
		%Oif		0.0	-81	-0,3
URO	22	Mean	0.3	0.2	93	0.2
(Enter)		50	0.3	Q. D	03	50
		N	10	9	10	10
		XICH		-28 €	0.0	-23.6
UNITP	22	Mean	ió4	241	124	111
(mg/dL)		30	49	365	80	97
1		N	10	10	10	10
I		14OH		132.5	195	74

General Footnote: [Statistical Test: Answe and Dunnett's test Transformation Automotic]

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

Table 8
Summary of Urinalysis Values for Female Rats

See Female			0 mg/kg/day Group 1	512 mgAgi da y Graup 2	1024 ന ൃദിപ്പിർ ദ്ദ ദേഷ്യാ 3	1536 mg/kg/day Group 4
	Day(s) Relative to S	tart Date		********	,	
UVOL	22	Mean	7.9	ti.B	£5	8.6
(mL)		so	6.4	5. t	3.0	4.1
i		N	10	tô	10	10
		NEW#		-12.3	-15.9	-149
p#1	22	Mann	84	ð,2	8.6	6.5
1		80	0.4	0.4	0.6	0.6
		N	10	10	10	10
		%E\M!		-3.9	31	0.8
9 G	22	Mean	1.637	1.635	1 028	1.030
		SO SO	0 027	0.023	0.011	0.013
		N	10	19	10	10
		ND#f		-9.2	-0.8	40.6
URO	22	Mana	0.2	0.2	0.2	0.3
(EUNE)		80	0.0	0.0	ΔQ	0.3
		N	10	10	10	10
		%CMF		0.0	0.0	40.0
UMTP	22	Meran	43	41	34	44
(mg/dL)		80	34	25	12	32
		N	10	10	10	10
		49DHF		-27	-20.0	3.5

General Footnote (Statistical Test, Anova and Durnett's test Transformation Automatic)

Oroup 2, 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingradient. Group 3, 1023 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingradient. Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingradient.

> Appendix A Individual Animal Clinical Pathology Data

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

```
General:
                                   not taken, not performed, not observed, or results not valid many
                    Ban
                    nan - many
Nod - 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 Homatology Values:

WB - whole blood condition
RBC - ted blood cell count
                    HGB
                                   hemoglobin
                    HCT
```

hemoglobin
hematocit
mean corpuscular (cell) volume
mean corpuscular (cell) hemoglobin
mean corpuscular (cell) hemoglobin concentration
red cell distribution width
platelet count
white blood cell count
absolute neutrophil (all forms)
absolute lymphocyte
absolute essinophil
absolute basophil
absolute basophil
absolute iarge unstained cell
absolute reticulocyte MCHC -RDW -PLT -WAC ALYM -AHON -

AEOS ABAS ALUC ARET

Individual Coagulation Values:

HEM - plasma hemolysis PLTP - plasma lipemia PICT - plasma leterus PT - prothrembin time APTT - activated partia

activated partial thromboplastin time

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

```
ABBREVIATIONS: (Continued)
Individual Clinical Chemistry Values:
HEM - hemolysis
LIP - lipemia
ICT - iccerus
                                 lipemia
icterus
                  icr
                AST
ALT
SDH
ALKF
                                aspartate aminotransferase
alanine aminotransferase
sorbitol dehydrogenase
alkaline phospharase
total bilirubin
urea nitrogen
                BILI
                CREA
                                 creatinine
cholesterol
                CHOL
                                 triglycerides
glucose
total protein
                TRIG
GLUC
                    TP
                  ALB
                                 albumin
                GLOB
CALC
                                 globulin
calcium
                 IPHS
                                 inoiganic phosphorous
sodium
                    NA
                                potassium
                   K
CL
                                 chlorade
Individual Urinalysis Values:
                QUAL -
                                quality (modifies color)
                                 clarity
                UVOL
                                 Volume
                                 volume
the logarithm of the reciprocal of the hydrogen ion concentration
opecific gravity
Glucome
                   pH
SG
                UGLC
                  KET
                                 hetone
                UBIL
                                 bilirubin
                                blood
urobilinogen
                  BLD
                  URO
                                protein
                UMTP
Individual Urine Microscopic Examination Values:

EPIT - epithelial cells

UMBC - urine white blood cells

URBC - urine red blood cells

NCRY - normal crystals

MICR - microorganisms
                                sperm
renal epithelial cell
mucus strand
                SPER
                REPI
                  MUC
```

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 (ONS)
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

Clanical Pathology Results for Soy Leghtmoglobin Previous On A 28-Day Dictory Study in Rata

Constitutions Months - From Mr. 600 to copy frata

Sex. Male. Days si Relative to State Days.

ft.	CINCLEFF RETHER CountY								
mg by day W	W.P	MB KW.	нов	।।एदं स्थ्य	MCA.	SETE	Menc.		
		աշխանդեն	tgvk.i		ttb	(इन्ह्रः)	18.18.1		
}	32	32	22	23	23	23	22		
"(x)t	OK	- 48	355	446 7	99.6	20.8	34.9		
1002	οK	* 49	13.2	615	500	198	34.2		
7003	OK	"65	13.5	45.1	58.9	20.3	3.6 5		
70 H	1 th	8 Le	161	12.5	Se .	300 -	33.0		
2009	OK	(3)	35.5	1571	58.6	201	513		
*1096	V.K	7.31	15.4	450	61.0	219	34.3		
7000	4060	- 66	15.4	(5.)	.50	20.5	34.2		
2016	υK	7.95	156	156	57.4	196	241		
7009	QK	" 19	16.2	15.8	58.8	20.8	35.3		
7010	OK	- 96	0.01	16.5	58.4	20.6	34,3		

Sex, Mad	Days of Relative to Start Dage

,	176	UTSIF REDUCTION	121				
անդանգոր	l ajud	PLT exter Fulls	Wist.	ANET	ALTM (Alg. Ball)	45578	4805 (GD/3 ₀ E)
			(x10 3/aL)			oxter Soults	
	> · · · · · · · · · · · · · · · · · · ·	17		2	<u> </u>	:3	<u> </u>
not	120	1108	15.14	2.29	12.11	ау	u B
*002	11 -	1118	\$1.88	1.52	9.71	0.34	0.23
1008	117	1217	[O 89	1.20	9.10	24.16	200
1904	12.2	1978	13306	3 1	1949	(1.2)	61
7003	123	12:9	14 23	1.34	1239	0.18	re*
2000	121	960	13.75	169	10.75	0.40	9115
1001	120	9/8]	12.24	1.35	[0.0]	0.35	013
19.41	122	1342	15.1.1	1.95	11 (8	# 22	(1430)
7000	120	\$246°	11 3	1.51	9.48	a 10	11.3.4
70[10]	123	144	1300	202	ધ્રાસ	4(36	0.33

Hospi 2, N2 marka the often advisors corresponds in 200 marks they of the active masselent (outp 1, 1024 marks his often advisors corresponds to 533 marks they active act

Utanical Pathology Results for Soy Legbornog John Preparation A 28-Day Dietary Study in Rata

Polytiches Active Similar latering Data

See Mile Hayes Relative to Start Day

0			
mp-lyr-day Denup I	Abas	ALDC	AREL
	(*10°34st.)	(x19/3/pt.)	rxt(r:3/pl.)
t	32	23	33
7001	fe }}	0.13	241.2
2003	0.06	808	225 6
0.0	12.0*	a 00	21.3.2
"(£u ∤	te tañ	a Files	233.5
0.6	0 13	613	2060
905	0.04	u 1,3	263.3
7601	o ja	0.00	233.9
700	014	0.00	197.9
3997	## <u>#</u>	(L)(6	1968
1010	0.10	tot	2252

Comp. 2. Si Long harden of test actionance corresponds to 250 mag harden of the active in gradient. Curren 3. 1024 may harden of test active active active active to 251 may harden of the active acti

Climical Pathology Residin for Soy Leghemoglobin Preparation | A 28-Day Dictary Study in Rats

Continues Answer Classical Process policy

Sex. Male. Digital Relative to Start Dave.

512	CPC/HFF RETS! Cond."								
Group 2	wb	RES.	RGD	18CT (**)	710.2.	MOTE	MCTIC* 1g ML1 22		
		ista pol c	15×E.1		1fL+ 22	(15g.)			
	22	22	22 27						
7021	ΘK	- es.	166	47.6	620	27 fi	348		
2022	ÓΚ	813	151	15 5	55.0	18.6	39 6		
2023	ΘK	1	153	41.3	58 S	198	33.0		
78024	UK	- 5%	14:	42.8	5× 9	20.2	34 ન		
1023	UK	102	119	4) 1	1 90	201	54.0		
7026	ÐK	7199	14.9	43.3	61.1	21.0	34.4		
7027	OK	K Gri	15-	16.2	57.1	19.5	33.9		
7028	OK	7.4	155	\$47	5*	306	3-1		
7029	OK	* 52	157	85.9	AL O	20.9	34.3		
7190	1080	7.34	157	466	62.4	21.4	34.7		

512	175	O'ESTERED Com	pd:		·		i
ան ին գույ գուն 1	жая	PLI	Wh)	ASIEU	ALYSE	45.0 (5)	4995
	1 * 21	6x10°3′id.>	oxto Sul.)	(200 April)	orly Ander	4x39 3/pl.)	extrebala
-	**	22	13	***		12	- 22
2021	12.	1335	1140	1.55	1199	0.28	0.10
7022	129	1136	16.79	2.38	13.33	98.84	0.35
1623	130	120	25.11	113	10(4	0.27	99
7024	121	1055	13.53	1.5	10.28	0.26	941
2025	13.7	1195	12.15	2.50	9 1	9.28	400
1026	129	11,75	13.87	109	1170	0.24	. GRO
1027	£1 °	1159	11 49	200	8 %	0.51	5118
2028	12.5	1300	291,57	216	1,81	0.25	012
7129	121	1229	1-95	2.36	11.26	14-27	013
*n3u -	121	1185	14 3h	<u>) 1</u> 14	114	e du:	n at

Occup 2, 312 marks the of test address communals to 250 marks the of the active appointed from \$1,1000 marks the of the address communals to 500 marks the of the office address communals to 500 marks the of the outer appointed thought 1300 marks they of the address communals to 550 marks they of the active manufact.

Christial Pathology Results for Sov Leghemoglobia Preparation | A 28-Day Operary Study in Rata

Constitute Angele, time we have ever but a

. 32 -

Sex Male - Daytan Relative to Stan Date

512			
mp) protesy	ABAS	ALUC	ARET
Ormp 2	extended i	այթ. Դրկ <u>։</u>	ester-Vjita
ľ	22	22	22
7921	D-13	n Ge	252.3
1022	0.13	613	2216
7023	12157	0.65	19* 6
1624	0.07	0.655	225 0
1075	D 186	II Cas	26.5
7026	52 (gs	9900	220 K
71827	ti tis	8.06	230.6
7028	1) 3.6	HC#	1619
7029	1584	0 fg	234.0
7020	13-63*	0.69	3.88.3

Courp 2 552 mg handre of test substance corresponds to 250 mag handre of the active properties. Descrip 3 5022 mg handre offers administrate corresponds to 400 mg handre of the active algorithms. Observ 3 1526 mg handre of test administrate corresponds to 400 mg handre of the active algorithms. Chancal Pathology Results for Soy Leghtmoglobin Preparation - A 28-Day Detaily Study in Rats

Confessional Australia Chambay Francisco francis

Sex Afrile Dayson Relieve to Start Dave

1924	CIPATIBLE PRINTED								
mgdq/dwy WB Grouge 3	wb	Kfa'.	HGII	HCT	WCJ.	SICH	80.317		
		oda kyt	1 g %€,1	(***	10.1	55 (DE)	1g)程.1 22		
	**	22	22	22					
141	ÐΚ	- 7.1	152	416	5 7.6	39.6	341		
1642	οK	n +=	161	16.5	60.2	20.8	34.5		
7613	OΚ	- në	154	#1.3	58.4	199	34.5		
7144	C.G.	- 12	140	16.7	80.5	216	343		
1115	-08	8,	361	16.2	58.1	201	54.8		
7046	üK	6.75	141	4o =	57.9	20.8	34 8		
7047	OK	- 4,5	15.5	15.5	63.1	208	343		
5048	ΘK	7,5	152	1.1.3	ei 2	21 h	143		
919	υK	"91	15.7	15 (1	26.9	19 K	54.K		
7090	··K	- 31	15:	160	58.9	29.2	34.2		

Ses. Male Dayso Helatne to Stat Date

1024	+*{	OSFFRED Som	pl?				
արկրչությ Groged			WB.		ALYSI WHI Apile	Atio (Klur) (Klur)	ABUS
			ext@ Sul.5				(MrAjiki)
	2.	-22		***	2-1	****	
110*	121	1366	\$1.55	164	945	9/25	. Olik
7012	12.5	1167	1492	20*	12.50	18 DB	0.16
7443	123	1228	12,44	2.31	9.52	0.37	(611
2011	130	1333	10.33	1.83	"ik	0.06	· · · · · · · · · · · · · · · · · · ·
7045	121	1002	9 46	1 54	* Ck3	4.59	0.13
7046	12.5	130	H 40	1 89	H-13	a 37	11]0
1041	126	1159	jocal	1.68	193	u <u>ə</u> j	: 040
*018	126	1232	14 21	1.08	18.96	0.25	13 11%
7649	129	F123	8.79	1.03	- u	# 22	440
7050	120	[160	9.86	2.12	- 59	01.03	1133

Hoope I StI rapha day often admine omispositi ii 200 rapha day of die schre upodiere. Gorge I 1974 ay hy dry often admine omispositi ii 500 raphy dry of the schre sepselata. Hoope I 1576 raphy often adminest computation 700 raphy day of the schre raphilism.

Chancol Puthology Results for See Leghetroglobin Preparation A 28-Day Dectary State in Ruts

Continues Address (1955-1961 Anti- 1983) Paris

. 54 .

Sex: Male - Days at Relative to Start Days

1024			
mg-landay Drough	ABAS	Atto*	ARET
,	taltii Bod i	1810 3 pt. i	ts) (c. 3cpl.)
ľ	22	22	22
7641	D 85	0.08	274.7
64	0.09	010	228 3
7043	0/06	0.06	293.3
*144	648	049	235.3
04.1	12405	016	222.1
7046	12.67	60.08	265.6
7616	OA"	0.05	243 0
048	1946	0.05	24511
1019	D (92	804	21.18
*050	0.64	0.04	244.2

Ostop 2, 512 regular des often adhaeuse corresponde se des regular des of the active regular desembles above 5,000 regular desse administrate corresponde as two agular day of the active expending desembles (design 1, 1536 regular day of the active expending desemble 1,536 regular day of the active expending desembles (design 1, 1536 regular day).

Claused Pathology Results for Sey Leghemoglobin Prevaration - A DS-Day Dictary Study in Rata

100327539004 A00824. (130.000) FACELLINES DATA

Sex State - Digress Relative to Start Day

15%	CECUME METHOCOMA							
mg-hp-tay WB Orang-4	W35	KRC.	HGb	17.714	MCV	Stritt	MCMC.	
	(क्षांस केंद्रों) । (क्रुंक्ट्रें)	(異情.)	{****	10.4	(pp.)	1等/程/1		
1-	22	32	22	23	2.2	22	72	
7163	0K	8.23	159	46.6	56.6	19.1	М 3	
2062	OK	* **	158	15.4	58.5	204	34.9	
* 143	OK	~ 59	159	15.5	59.9	21 ()	33.0	
7064	OK	36	161	17.1	63.9	21 8	34.0	
1066	QK.	84	16.2	16.3	59.2	296	34.8	
*166	OΚ	* 40	140	44.X	60.5	2012	33.3	
96	4060	* 64	139	15.5	59.6	208	34 0	
719/88	OR	-1/2	14.7	151	30 ;	203	34.7	
2009	QK	K1.6/	16.1	169	55 c-	201	54.4	
2020	OK	\$8	161	15.4	601.5	21 7	35.0	

Sex. Male Boys : Relaine to Stat Date

15.40			CPC	DEFARTO Com	Ķ.		
ուր եր աշ	WB	RPu"	Hop	FIFT	740.	1586	SICHC*
Ginno 4							
I		tal0″6ad.>	1歲八萬-1	₹**	+11.2	(\$7 45)	192-12.1
-	**	12		**			22
161	OK	823	159	10.61	50.0	193	된
7062	÷κ		158	45 3	58.5	29.4	34.9
"(XG)	· K	* 50	159	45.5	59.9	21.0	3.5 17
2061	QK	* 16	161	in (650	21 ×	34.2
*(65	OK	784	162	164	\$9.1	23.6	34.8
1966	UK	*40	140	14.9	1kJ 5	263	33.3
1667	ÓŘ	. 64	13.0	15.5	406	208	140
1068	OK.	- 62	15.7	15.1	39.2	20.5	3.1
2669	ΘK	k i a:	161	66.9	58.6	2.01	94 A
7020	ÐΚ	- 584	(7.)	49.0	69.5	28.2	150

(1994) 2. NE rigita filip of the adolesce corresponde to 250 rigit kg/dep of the infive improduct.
(1994) 1. 1026 rigit grits also of the artistates extraporate to 500 rigit gridey of the within hypothete.
(1894) 1. Ne rigit gridey of the arbitrates corresponde to 750 rigit gridey of the active ingredient.

. 35 -

Classical Pathology Results for Sew Leghermoglobin Preparation - A 28-Day Dictary Study in Rita

Desirations America, Tiplical Sans, Englishes

. 36 -

Sex: Male - Daytor Relative to Stan Dage

1536 mg-kg-stay	Anas	ALU:	ARET
Osmp-I	121053-3-1-1	(x10°3°pL)	ester3/րել
1	7.5	33	:2
7061	0.06	606	283
1001	0.69	0.04	238.4
053	0.23	1109	320.6
7064	0.06	640	3199
2066	0/12	0.00	242.2
7066	0.65	tin)*	224 8
7067	DOG	n14	2499
7068	0.11	015	1945
7000	0.04	und	235.2
7870	13 125	0.06	214.2

Course 2: 512 ma harder of test sebenance corresponds to 250 may harder of the active suggestion. Uses pt 1 (102) ma harder of test sebenance corresponds to 500 may harder of the active suggestion (Script 1 1550 may harder) of total sebenance corresponds to 750 may harder of the active suggestion. Clanical Pathology Results for Soy Leghetmoglobin Preparation | A 28-Day Dietary Study in Rata

Confidence Andrews - Charles Forth April 2018

Ses Femele Days (Rednive to Som Date

n	CECULE RELIC CONS.								
mg-kg-day Doug-t	WD	WD REC	нов	HCT	MCY	Mru -	мене		
·		ester sopt c	tg:vk. i	(4.)	1 fl.)	spg.i	18/41		
	22	12	22	<u></u> :	***	22	22		
7011	+3K	7.71	; 4 7	43.5	56.4	204	363		
2012	ωK	*92	35* - 7	118	5* 1	29.1	35.2		
701.3	OK	-22	14.6	62.4	58.8	20.3	34.9		
70(4)	UK.	- 12	150	14.4	57.5	\$9.2	353		
101.5	UK	3.3	150	0.5	412	No.3	M.*		
7066	4010	7 11	1.4.6	42.4	3")	14	34.4		
702.7	СK	7.01	161	MK :	161	>04	363		
7018	⊙ K	47.	156	45.5	38.6	201	113		
2019	OK.	- 6-	124	13.5	.w. ·	291 .	35.5		
7820	OK	7.33	147	41.6	55	200	35,3		

Sex. Female - Dayta) Relative to Start Date

lt .	17	ODSTERESBURGIN	tij i				
mp krobo	HDW	72.1	ያለብቃ	ANFI	ALYM	A\$408	ABAS
from t	(50 (30)39th	tx49/3/pl. :	(x30°3/nL)	(x10/37d.)	alti diko	(zitt igd.)	extersolar (xtersolar
-	**	12	·····		**************************************		<u> </u>
2011	11:	13%	970	1.42	" vj.	aln	11186
7012	10.3	11"3	88)	1.49	€ %	n 21	0.10
~68.3	111	1282	9.63	1.65	7.43	n Vij	· 911
268.1	11:	1/04	2016	1.55	N/1	0.14	20 180
2013	11:	1217	8.53	200	621	0.13	(10)
*0i6	11.6	1124	11.48	1.80	440)	(1.4);	01"
98.7	108	ກນ	×91	1481	• • • •	913	0.13
*008	123	1/4/4	11.95	1.38	1044	0.19	81]]3
7819	111	1373	13.21	i ti	(6.9)	0.58	0.09
7020	11 \$	1399	* 89	131	6.20	0.21	(1)

Dates 2. N2 tracks the offers advance consequents to 25 trackets, of the netwe agreedent Gorep F 1925 marks objective attended extragolates. On agriculture of the attended extragolates (60 agriculture of the attended extragolates) (60 agriculture of the attended extragolates).

Canical Pathology Results for Sey Leghemoglobin Preparation - A 28-Day Delany Study in Rata

Dadyminther Action of the College Date

- 38 -

Ses Femilie Days of Relative to Sain Onte

» l.	***************************************		i
eng by day	ADAS	ALUC	ARET
	(810/398.)	ixter3/jita	txl(r:3gil,)
1	22	22	32
7011	nas.	: nu)	151.8
70t 2	D fig.	0.04	1928
*nt3	on <u>t</u>	900	205.3
"(1)-4	1+44	ucs	2850
at.	12.03	60)	243.8
*916	12 (13	905	153.5
THE T	13/83	414	226.8
7018	121)5	866	252.5
764.9	D-137	0.00	194.2
7820	0.02	9.04	2220

Ostop 2, 512 mg hg, diej offent indinance contequents in 250 mg hg, day of die neller ingredient. Gazep 3, 1024 mg hg, diej of ten nebrance conseptuate to 300 mg hg, day die nellen nebrance conseptuate to 300 mg hg, day de die nellen nebrance conseptuate to 300 mg hg, day de die nellen nellen nebrance conseptuate to 700 mg hg, day de die nellen nellen nebrance conseptuate to 700 mg hg, day de die nellen n

Classical Pathology Reselts for Sew Leghermogletin Primaration - A 28-Day Octory Study of Rats

Sugarational Assessment account for the coope first a

Sex Femilie Days (Relative to State Date

510	CENTIFY RETURNATION								
mg-lg-ray Ozong-Z	W 19	RRC.	нар	1107	MCA	PL 15	X0.34C		
, l		स्थित स्थान	1度特別	ther i	181.4	(pg.)	19,541,0		
	2:	22 22	22	22	23	32			
7031	÷κ	8.35	162	45.4	54.4	194	35.6		
2032	0K	8 12	36.9	10 S	563	20.6	33.6		
7013	VIK.	813	155	14.5	53.9	391	34.8		
*694	OK	89	(7.)	169	58.3	204	나이		
1635	QK	u,	1.5	14.5	6) ()	21.5	13.3		
7036	UK	7.93	165	46.3	58.4	20.8	35.5		
7032	ÐΚ	8 48	163	16.4	948	19.5	35.6		
2048	ÐΚ	T No.	162	in i	39.2	207	363		
21897	UK.	W 21	160	47.7	55.1	204	35 1		
*10.00	COK	-61	157	1.1.3	58.2	20.5	35.3		

Sex Fernale Days of Relative to Start Date

912	128	PERFECTION	pl'		į	1	I
ությեն մեծ Մոտու 2	нрж	HDM LT1	Wis.	ANEU	ALYM	AM) (S	ANOS
	1. ⁶ -91	(इ.स.च-अध्यः	ext@Sul.s	(x10/35aL)	i kala Audo	(x89/3gd.)	(Xb) 3 gL)
	**	1+ +-	13		***************************************		÷
2001	11.1	1067	11.74	1117°	10.74	0.32	1113
7032	113	1381	1943	0.99	976	1179	(11)
7033	111	\$199	15 00	2.2%	1315	0.32	69.70
2034	10.3	1112	9.30	1.45	11.07	0.21	11 (1)
2035	113	13/8	12.45	2.38	D 15	4.3"	0.69
2036	H.4	12%	11.46	199	R SO :	a Vi	11 10
1037	108	1107	12.98	1.9	10.55	0.26	111
1038	119	1975	Ju 91	0.74	9,90	0.32	9116
7839	112	1648	10.62	1.20	к.8	934	: 01"
2640	11.8	10%	12.10	1 K4	9.10	9 24	** ** **

Userp 2. NO rapits the of test editionanc commencia to DN employing of the wifer agreebent Gorqo 1. 1026 agrils the office substance consequents of 600 agrils and of the other appealant Ostap 1. 1500 agrils they office substance corresponds to 700 agrils and 600 active agreebent.

Classical Pathology Results for Sov Legbernoglobin Preparation: A 28-Day Dogram Study in Rats

To himsball American familian Earliching Data

. 40 .

Sex Female Days of Rednive to Start One

512		i	L
media day	ABAS	at.ur	ARET
Drungs 2	(811)*3-pd.>	1819:3/pLs	ester kata
ŀ	22	32	22
7031	0.6	11.06	1558
(3)	0.03	0.06	199.4
7033	040	819	205.1
2634	41113	6125	163.2
035	0,00	0 (n	214 8
7026	0.06	1107	222.9
7837	0.09	0130	133-1
1038	047	040	137.0
*(139)	0,02	सार्छ	(810
nuo	0.07	866	2/0/3

Ostop 2, 512 tegit profession membrane contributed to 250 tegit prices of the active in grachest Coupp 1, 1020 tegit prices of the active in grachest Coupp 1, 1020 tegit prices of the active agreedules Coupp 1, 1030 tegit prices of the active agreedules Coupp 1, 1030 tegit prices of the active agreedules to 700 tegit prices of the active agreedules to 700 tegit prices of the active agreedules.

Claused Pathology Results for Soy Legbernoglobin Preparation - A 28-Day Dictary Study in Rats

sugarthesis Asserts of Fibrian Code Cody Date

Sex Female Dayse) Redulive to Start Date

1624	CDO-DIFF REFUC Com/C								
mg-kg-day Group J	WD	REC.	Hill	BCT	MCV	5 र ाम	NO. HC.		
		exto equi (gré,)	18/48.1	5 ** *	18.	(FE)	(別/表)		
~~	27	22	55	22	23	20	22		
*051	19 K	90	3.53	12.6	56.8	20.5	36.6		
7052	OΚ	*61	147	14.1	.080	20 6	35.5		
7053	9K	- 51	156	14.7	56.5	198	33 0		
7654	V/K	X In	3.4	16.3	55.8	195	3-4-1		
1653	OK	`8 [¬]	152	13.2	35.0	194	35.3		
7886	OK	7.91	157	450	56.9	19.8	34.8		
705*	ÜK	ેલ્વ	154	43.6	57 D	202	35,4		
7058	OΚ	802	147	445	55.4	193	45.4		
*059	OK	***3	161	15.9	59.1	20.8	35 1		
1000	OK	8.35	163	466	\$9.4	199	35.5		

Sex. Femide Days) Results to Start Date

1024	175	UMDEF REDECTOR	Δ1);		į		2
mpila day Omne 3	RDA	HDW FET	Wb."	ASFU	81.YM	48378	AIXIS
	60.05	(x10/3/6L)	exto Suls	oxi0/3qda	oxBC 3qd	estantinal.)	exter Sala
	?	•••		22	2.3		
"1951	11.2	1,284	191	1,125	r 0)	a 29	11] [
7052	11.2	1293	3 41	1 3*	6.53	n, 233	0.13
175.3	119	1220	12.90	2.9	944	n é é	9 [9
7051	11.5	1863	13 ^K	2.33	H-54	ú <u>)</u> (2	48134
7055	111	1334	\$ 29	1.21	6.65	ი≃5	0.08
2056	11.5	1162	15 18	: 62	1216	u 40	11.23
1081	112	11.'8	12.42	14,865	11 (4)	0.21	u 15
7058	Ho	1906	17.73	3 02	1388	n Ja	3018
7092	11.0	1946	13.10	1189	11 46	0.38	0.20
7097	189	1363	× 10	1.00	6.76	015	1115

Divered 342 mptg the office allowance commenced to 240 mptg. Ling of the allow aspectant Group 1 1025 mptg, the office allows consequently to 500 mptg, Ling (400 mills reported through 1 1025 mptg, the office allowance consequently to 500 mptg, Ling (400 mills reported through 1 100 mptg, they office allowance consequently to 500 mptg, Ling (400 mills reported through 1 100 mptg, they office allowance consequently to 500 mptg, Ling (400 mills reported through 1 100 mptg, Ling (400 mptg, Ling (400

Classical Pathology Reselvs for Sew Leghermoglobin Preparation - A 28-Day Dictary Study in Rata

Indianas Asimo tinomi kataling hare

Sex formate Days o Rolative to Start Onto

1024 mg/)g/day Orong/3	AlbAs	W'er.	AREI
	(410° 3-94), s	32 (8/18)	rst(r:3-pl.) 22
*651	0.03	0.03	180.9
1052	6) f)3	870	187.5
653	0.96	H 05	1105
2054	e 05	0.08	16612
055	0.08	Buj	l×0×tl
7056	15.33	u Li	1'8 *
765*	on*	0.00	203.0
7058	637	#H	164-4
1039	0.05	0 112	113.4
*060	Ð fi3	8.04	174.5

Orași 2, 512 îng ligislej officii adminisc conceptuale à 250 îng ligislej officialitie nigredieri Garap 3, 1923 îng ligislej official adminisc corresponde to 500 ang ligislej of the adminiscrptulari Garap 3, 1520 îng ligislej official adminisc corresponde to 700 ang ligislej of the adminiscrptularity Canical Pathology Reselts for See Cophemoglobia Primaration - A 28-Day Dictary Study in Rats

Controlled Assert Change thereby beta

Sex Fernise Dayter Redam e to Sour Oute

153%	CIPATHER METHOL COMMA								
mg/kg/stay Dipmp-4	WB	RPC.	HGb	19.77	NCJ.	MA	22 N. 34.		
		12(0 figh.) 1g/k.) 22 22	1g5R.1		141.7	22			
-	27		22		22				
7071	υX	. 7.	147	42.2	55.1	19.4	349		
2672	68	754	14.1	113	36.4	12.7	34.8		
*0-3	9K	7.32	15.4	143	61.2	23 8	34 4		
7074	0.0%	* 4%	350	12.3	56.8	50.3	35.6		
1023	138	~ Q.S.	150	HR	35.4	\$9.°	35.5		
14*6	1380	7 27	157	43.9	60-4	21.6	35.8		
7057	0.50	812	165	17.3	50.11	316	35.5		
7078	3K	7.67	160	16.2	602	20 R	,945		
*0*9	1.68	"82	132	13.1	55.1	194	35.3		
*(80)	eg:	*31	14.9	42.0	51.5	203	35.3		

1(80)	- 0%		14.9	4,751	. 3:3	. 2013	. 27-4
ex Fanale 1	ayoo Realise to:	San Date					
1<5.	1.6	OTSIF RED TOM	(vi ⁾				
material in the control of the contr	REPAY	F9. [W79."	ANET	ALYM	AMA IN	A1808
	154)	(x10°3°aL) (x10°3°aL)	(x10/3yal)	ixf0.39d.c	(x8609)du	CG0/3gLi	
-		£-q	#7 #7		***	<u></u>	V-4
`(£ ³	124	1052	12:22	2.68	я ' (0.28	943
7012	33.0	1262	7.01	0.79	5.94	11 (3	01:
*073	113	1514	17.13	448	12.09	n \$5	915
2024	11.6	1,335	4.19	1 10	196	9.00	+1413
7013	11.0	1366	10.71	188	9.28	619	9 69
2666	199	1,869	}(cXn	1.12	9.35	(t.5)	910
2102	11.	1195	151 58	1.23	864	(1_5)	+126
7818	(82	1299	[413	0.92	1209	0.21	#T
7019	11.2	1153	- 19	0.79	673	6 3	0.09
71 6 0 ×	120	1052	A Ch	1.33	465	667	- 6] (1

. 13 .

Disciple Net registable of the distance corresponds to 200 mg/kg/day of the utility improduct closes. I 10,50 mg/kg/day of the utility improduct closes. I 10,50 mg/kg/day of the utility improduct (2000). I 10,00 mg/kg/day of the utility improduct. (2000). I 10,00 mg/kg/day of the utility improduct.

Clanical Pathology Results for See Leghetmoglobin Preparation A 28-Day Digitary Study in Rate

Contemporal Angele. Tire- as Latteling, Pata

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Sex bemole Days (Relative to Sear Date

1536 mg-ka-day Dyngo 4	ABAS	ALUC	ARET
	18187 अनुत्री, र	(MPC3'pL)	oder35pt i
ŀ		?2	12
150	t) (1¢	n 04	239.17
7072	0.02	8.01	1'92
7073	94	914	254.5
7074	ent	603	164.1
107,5	0.05	0.06	1329
7076	6.65	9.04	1160
74)**	URS	0.06	1607
0.8	o jo	9110	155.2
1019	0.03	0.04	1907 (5
(81	1) 02	8102	238.7

Outple Sile replacing of the solutions continued to 250 medicines of the active nanodest Gospi I (650 medicines) of the active nanodest Gospi I (650 medicines) of the active nanodest Gospi I (650 medicines) of the active nanodest corresponds to 750 medicines of the active nanod

Classical Puthology Results for Sey Leghemogletin Fregueties: A 28-Day Detay, Study in Rata

- Indiana Anne Cina a tata 1977 Lete

Sex Male Dayter Relative to Start Date

o ing≪g day	PHEM	P).15°	iner	14	ÄFTT
		1	1	(200)	(seu)
	29	29	3		29
101	None	Nepe	yexx.	111	29.5
2002	None	Name	Som	1966	13.6
7003	Nime	None	None	10.3	20.5
3004	24 crose	None	None	1654	25.4
i (mg	None	None	Nice	16:5	***
1006	Newser	Neile	Note	161	22.5
700	Nima	New	Nexa	31.1	17.5
71.038	Nine	New	None	36.9	20.2
31.029	None	None	Nove	808	198
50[6	Nice	Seile	Seese	\$0.6	19.1

Sex. Made. Days is Reliance to Start Unite.

M.					
ng Egolay. Organ 2	PH251	PLE	FPC1	PT	APTI
•			:	lwei	19401
	29	29	⇒ ;	3>	29
79,521	Nine	Noue	Note:	III	21 7
7/02	Norma	*Sinne	Norte	106	34.6
7/03	Semi	Sem	Neer	10.5	(Ye)
7004	Nome	None	None	te t	19 "
7025	Nume	Nive	Nicce	10.8	34 0
70Q6	Nicese	Nope	Nerv	[6]	21.4
7007	Norte	None	Noor	11: 5	21.2
1008	None	Sene	None	11.3	22.6
7009	None	None	Nece	[R.*	22.4
7030	None	Norte	Neeze	180	17,9

Comp. 2. 512 mg. kg. 421 of the indexage confequencies 290 mg. kg. day, of the antise ingrodiest. Comp. 1. 1024 mg. kg. day, of one indication correspondence 900 mg. kg. day, of the antise agustical Grap 1. 1356 mg. kg. day of one indication correspondence. The mg. kg. day, of the active angies done. Clement Pathology Results for Sey Leghermoglobin Preparation - A 28-Day Dectory Study in Rata

Charachas Anassa Crana, an Abbology Laba

Ş)ex	Make	Day(*)Relating to Start Data
•			

1604 mg/kg/day Gracqi 3	PHEM	P\$.33*	196-1	н	ÁFTI
		į	:	(2001	1 500}
	29	<u>*</u> :	29	÷	29
7/541	None	None	Nex	103	11.9
(04)	?icex:	None	Noor	109	27.8
7643	Netter	Name	None	183	21.9
Tel-1	None 1	Neme	Norae	[16.7	21.0
7(4)5	None	Neuz	None	[0,9	21)
TURA	New	Nere	None	10.4	22.4
(4)	Noras	None	Nemar	Lu 3	374
3048	Nettat	None	Norte	to-	シッ
1949	Nesse	20000	Note	106	278
70,686	Norm	None	Need	10.9	264

	Sex	Most	David	Relative 33	Seritors
--	-----	------	-------	-------------	----------

1536			i		
make day	1.HF24	71.17	PET	ध्र	APTI
संस्कृताः व		1	:		
			1	19661	19607
	29	29	5	39	29
7063	Nuese	None	Nex	{(; *	35.2
7062	None	New	None	10.5	3× 0
(46.3	Norm	Sono	500	10.5	25.2
3064	None	None	None	10.1	23 n
7065	Norm	None	None	10.6	20.8
2006	Norw	New	None	1112	21.8
20m2	Nipero	None	None	146.3	: ' R
1008	Noon	Sens	None	10.3	20.09
7069	None	None	None	109	22.6
7074	Name	None	New	16.7	23.3

Corep 2, 512 fig. Lycky of four additions confrequence (20 ring by day, of the active digitalised faces). The core of four additional extrapolated in 900 fig. Lycky, of the active digitalised faces of the first and confidence of 550 fig. Lycky, of the active digitalised cores of 150 fig. Lycky, of the active digitalised cores of 550 fig. Lycky, of the active digitalised cores of 150 fig. Lycky, of the active digitalised cores of 150 fig. Lycky, of the active digitalised cores of 150 fig. Lycky, of the active digitalised cores of 150 fig. Lycky, or the active di

Classical Pathology Results for See Leghemoglobin Preparation | A 28-Day Diction Study in Rata

Individual Answel lists of voted boy late.

Sex Bermile Dayini Rabitote in Sixti Date

o mg.kg day Omraji I	PHEM	b172.	PRC*I	H,	TITE
ì				(500)	(sec)
	,¥1	36	30	<u>R</u> 1	30
7013	None	None	Nexe	98 .	22.6
101.2	Nicese	Nets	Neer	16.4	23.4
7013	Nemer	New	None	34161	18.6
2014	Norma	Nens	None	101	20.3
1015	Negar	Sept	None	160	23.8
7016	Notice	Note	None	101	26.8
50) 2	Nitro	Kenw	New	99	196
7018	Norw	Nene	None	103	22.6
189	North	None	None	98	19.2
7020	None	Some	Note	10 I	21.3

Sex Female Doytor Relative to Start Date

512 rog/kg-day stroop 2	148571	PLUP	1711.71	rī	AP17
	*1	1).		19401 :	† MC1
7031	Nice	None	New	10.0	1*3
5.02	Percen	None	Nixa	9.1	21.4
1003	Nece	New	Sirre	0.0	\$63
*03.1	None	None	None	99	29.0
7034	None	None	Nese	9.5	181
7036	Normal	Name	Notes	100	21-1
7047	Street	Neme	None	96	794
10.08	Stone	None	Nece	[1/1]	180
*039	Neege	Nene	New	96	190
TOMB	None	None	Note	10.1	22.1

timp 2.512 nghg day of na ndananc omengadan 250 nghg day of the atten ngustant. Comp 1.102 nghg day of the atten agustant composition of the glygiby of the atten agustant of the 200 nghg 1.1020 nghg day of the atten agustant of the 200 nghg 1.1020 nghg day of the atten agustant.

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Claused Pathology Remitte for Sey Leghemoglobin Preparation | A.28-Day Dictory Study in Rata

Individual American Living as Advictory Lata

841	Lennale	Dectat	Rolstoneto	Store Tarte

1024 mg/kg day Orong 3	igness	(PLIP	ស្រីកា	មេ	ätti
		į		(200)	(386)
	¥1		3)	9,	¥i)
161	Sione	None	Now	186	⊃a .
1052	None	None	Neec	10.1	2" 3
1063	None	None	None	93	149
064	Norw	Neme	Noon	94	13.1
ងផ្លូវ	Secre	cue	Note	10.0	213
2056	Minte	None	None	164	21.0
7097	Norm	New	Neoe	0.9	23/8
168	. ACRESO	New	Note:	9: .	(5.4
វាក្សម	Norm	None	Store	162	38.3
21 (6)(1)	Norm	None	Note	10072	5 2

Sex Female Dayis Relative to Start Date

1536 mg kurday	P1024	FLSF	nei	PŦ	AP17
ilteop 4				1,980.1	e seni
	₩)	16	ų,	31	34
2003	Nee	Neik	yen	9.7	18.2
2072	Nome	Now	New	9.9	2013
1003	Noon	New	Nove	9.1	1 6
707.4	None	None	None	1600	169
2075	Mostar	Neue	Nore	67	18.3
5006	Norm	None	New	10.1	23.6
7007	None	New	Nese	9.7	20.1
and R	None	None	None	100	20.3
าาสม	Note	Neise	Not	9.5	78.8
1060	None	Nene	Note	9.9	19.8

Outp 2 (12 tigdig des often nibrane outerpredon 20 tigdig des othe nibra tigdig to Comp 3 (102 tigdig day often utbranes companies e 163 tigdig day of the nibra tigdig do Outp 3 (156 tigdig day often utbranes companies to "Foling Lighig of the nibra signification Clausia) Enthology Results for Sep Enghanneglobin Preparation | A 28-Day Dictary Study in Kita

individual Adams, from a factoring large

Sex Male. Dapass Relative to Start Date

4+			•	Greets Chem Phy			
mjeksedin Great I	HEAT	LO ^s	ICT	AST	VII	SCH	ALKP
				(UL)	(U.L)	37Li	+U3,1
	22	22	23	22	.22	22	22
(41)	Trace	Note	Nime	SPH	29	NPH	884
1002	lines	Soute	Section	SPH	N.S.	SPH	16:2
1,623	Trace	None	Note	SPH	23	NPH	166
1494	None	Nein	New		26	103	241
1146	None	heim	Note	8.	Q 1	7.	2.0
11,645	Iroue	None	None	NPH	39	SPH	181
70,07	Kome	Nime	Sime	7.7	30		87,3
3000	Trose	None	None	NPH	>	NPB ;	180
7009	Nuoz	None	None	70	25	8.4	758
*010	Person	Signer	Note	65	26	6.6	172

Ses Male Dayco Relative to Sun Date

ı. 1				Olympian Cham Plea			
ng kasta Grenn t	LIN	18.73	CREA	GOL	ផ្សេច	tinx,	ÎF
	ragesil.)	≀mg.dL+	। १९५५ स्ट्री. ।	क्ष्यद्वीत	ong-dl.)	माहनी.)	igytt.s
ŀ	15-7	11	37	· · · · · · · · · · · · · · · · · · ·		22	***
11921	4119	1.3	423	- 18	53	113 .	6 i
21.02	uts	l i	0.23	105	K2	K2	56
2068	ac19	9	31 (2)	9 0-8	6*	18	49
11763.8	4116	12	0.24	"3	90	35"	6.2
70425	a in	11	0.23	-,	50	99	60
7006	0.36	16	et <u>2</u> 3	89	- Qkii	120	56
11:97	411.4	q	81 <u>2</u> 41	15	55	9 <u>2</u>	5.6
1.635	917	ĸ	21.22	68	72	X1	40
7109	n 1 \$	11	0.31	7.3	- 3 '1	96 :	54
74)344	n [-t	11	0.22	69	62	3/3	5.0

Comp. 2:512 mg/kg des often informace correspondere 250 mg/kg/des of the write ingestant.
Comp. 1:1024 mg/kg/des of this informace corresponders. 550 mg/kg/des of the active ingestant.
150 mg. 1:1024 mg/kg/des of the active indentical corresponders. 750 mg/kg/des of the active ingestant.

. 49.

Octobral Pathology Results for See Legislanguckin Preparation - A 28-Day Dietary Stady in Rata

Species and Allered Condition Exploring Cons

Sex Male (Dayes) Relative to State Date

Ď				Okresta Ozm Pla			
mg-kg-day Group I	ALB	GLOB	CALC	tpis	NA	K	٦,
	เลาสัยส	الملكحوا	(Refrojt)	(mg/dl.)	annett:	caused:L+	(mass), (
	22		33	33 67	27	53 F.2	7.3
70(4)	3.2	29	167	SPH	143.5	491	102 5
1.45	.5 [2.0	10.4	164%	10.6	5.41	101.5
1(2)3	31	2.8	19.5	NEI	1 #1 9	5.02	1000
71)452	31	3.1	10)-4	8.6	142.0	4.96	101.5
100)	3.2	18	10.2	90	140.5	1.95	101.1
1,6%	3.1	2.9	1975	SPH	140.8	5.32	101.8
10.657	3.0	26	168	83	138.9	4.91	940
2008	3.2	3.8	19.3	SFR	111.9	4.65	102.2
1009	3.3	31	108	8,3	111.3	3.22	100 \$
1010	31	2.8	[104]	89	140.5	4 82	101.4

Course 2.512 mg kg die of toe udstande omtespredere 201 mg/kg/day of the active argenteer.
Outsp 1. DC2 mg/kg/day of the advance composited to 900 mg/kg/day of the stative argentiest.
Corap 1. TM mg/kg/day of the advances consepted to 700 mg/kg/day of the active argentiest.

Clinical Pathology Results for Soy Legicanoglebia Preparation | A 28-Day Dictary Study in Foto

indictional America and a sector by Lucia

Sex Male Days of Residence to Stan Date

912	Olympia Claim Pka									
mg-kg-day HEM Green Z	HEM	L.IP	ic T	AST	ALI	SEAR	ALKP († 2.)			
				445	41.11.1	र्दश्रीत ।				
1	22	22	22	23	20	27 :	22			
7021	None	New	None	70	5)	RO 3	792			
10/22	None	Stone	Scotter	85	25	19	245			
1023	Er noc	None	Nere	NFII	26	NHI	218			
7004	None	North	Nixte	76	24	*6	544			
1025	None	Siene	Norw	K2	29	lio i	382			
1020	None	None	None	7.6	71	7.1	231			
30/27	None	Norse	Name	*1	3,5	R.A	35-1			
1028	Nesse	None	Norm	68	.4	28	3.6			
*029	None	Nene	Nume	63	2-	91	190			
10000	Ninne	Norma	Niner	92	41	8.2	237			

Ses Mile Dayso Reading to Sun Oale

512				Olympia Olym Pka			
make by	RILI	BL5/	CREA	tTiskl.	1៧៨	GLIC	11,
Brough C	engefi.>	(mg/dk.)	(१६६ थी.)	(ज्ञापूर्वीतः	(mg/di.)	-mg-dL)	+z):0.1
ŀ	22	22	22			₫ .	<u></u>
11,21	417	11	0.24	80,	7.1	144	a 2
7022	0.29	- 11	0.29	~:		197	5 "
76/23	(417	q	11.25	9:	65	114	5.4
1024	0.18	1.0	024	51	3/9	100	61
1025	0.18	11	0.24	. 53	65	96	60
24 (36)	915	13	0.29	13%	(e)	90 :	< 9
16721	015	12	0.23	55	61	1(0)	5.0
1008	1115	"	0.23	29	92	91	5.3
7009	019	y	0.24	ųς	85	94	6.2
2690	017	12	0.23	76	66	DI :	5.

Course I 512 marks she office independent consequentive 290 marks, only other within appropriate Course I (1924 marks) of the water ingredient (1924 marks) she water ingredient (1924 p. 1936 marks) of the water ingredient

Classical Duthology Residus for Sey Leghemoglobin Preparation A 28-Day Dictary Study in Risa

Individual August 1998 at 1996 Page Lang

Sex Male Dayts) Relative to Start Dete

512				Olympia Chin Plac			
ing kasaby Grein 2	ALB	GLOB	CALC	TPHS	NA	K	٦.
1	المائدون	rg.vdt.≠	(regult.)	(mg/dL)	anned/L)	(decemb	(masse).)
ļ	22	32	17	2.3	**************************************	~	31
1021	3.4	2.8	110	93	142.5	420	100.8
1022	.51	2.6	10.5	8.3	10.6	5 (05	107.2
1023	3.3	31	10.5	MH	140.7	5 27	101.5
11/24	3.2	2.9	10.3	8 }	14) 3	533	[43] %
1/25	λ1	24	10.3	944	10.9	5.35	102.6
600	3.1	: 8	10-4	86	1420	5.34	1926
6/2*	i i i	3.0	fot	8.8	140.4	5.25	192.8
628	3.0	29	10.5	85	143.2	5.66	102.2
1029	3.3	2.9	103	K 9	140.5	4.73	1907
7000	3.2	2.9	103	8.4	1430	5.78	183.9

- 52 -

Comp 2: 512 mg kg dan often sabasane corresponda o Norma kg day of the same argenters.

Lamp 2: 1022 mg kg day of the sebessate corresponda to 500 mg kg/kg/kg of the salive argenters.

Comp 1: 1750 mg/kg-day of the nationate corresponda to 750 mg/kg/day of the same argenters.

Chascal Futhelogy Results for Sep Leghemoglobin Preparation | A 28-Day Dictary Study in Rua

constant the C. American constant and starting for \hat{x}

Sex Male Days (Relative to Stan Date

1024				demotes Chem Plea-			
madadin Green J	FIEM	f.IF	ILT	AST	ALI	\$120	ALKP
				94(1)	03/13	(04.)	(1/2)
]	22	32	22	23		* *	72
340	Noos	None	Norm	кi	54	- ;	181
1942	Some	None	hann	76	28	- <u>-</u> - `	30
7043	Truce	None	None	NPH	24	874	193
7144	Nome	Мори	Note	86	28	130	22.7
1045	1000	Seni	None	SPB	30	NPB :	295
1046	None	None	None	{c } 4	32	KB	236
10AT	Fireta	Norm	Nixw	V#Ht	29	NIPH :	157
机械	None	24009	Humo	×*	25	6.9	37.
1049	Trace	Note	None	NFH	31	N141 :	244
*(50)	None	North	Nimer	- 3	31	20	16-1

Sex. Malo Dayyor Relative to State Date

1021			1	Streets Claim Pkg			
mg kayday Green J	RIL.I	HC73	CREA	:38.4.	IRIO	OUX,	(P
	mæsil.2	(mg/dk.)	(mg/dL)	(mg/dL)	(Aleguo	emgsdl, t	(#XB.)
	91 ***		*1	=	<u>=</u>	<u>=</u>	73
76-13	949] P:	0.22	' ')		100	52
2642	037	9	0/22	K 3	540	Re⁻ :	5.3
7043	81 f *		0.25	7()	67	101	5.5
7044	018	De .	0.23	73	50%	₩ .	63
1043	0.15	11	0.26	91	63	109	40
10.46	4.30	12	0.25	92	,	124	56
,045	#(E	4	9.23	1;	58	RC .	6.1
11-48	8115	12	0.23	16	63	83	60
1649	a Dr	Я	0.26	(ق	41	99	61
71990	11.20	111	0.20	75	4:	136	61

Comp.2. 512 rights are often informed correspondence 200 rights, they of the letter important.

Group 3: 1072 traphysion cities informatic correspondence 300 rights also of the active important.

Group 3: 1076 rights also cities informatic correspondence 300 rights also of the active important.

Classical Pathology Residts for Sep Leghemoglobia Preparation | A 28-Day Dictary Study in Rata

Distribust Animal Contras Participal Late

Sex Male Days of Regimes to Start Date

1024				th ac e Oen Pla			
makadn Grego J	ALD	GLOB	CMA	tens	NA	K	CL.
,	1 <u>2 vill.</u> 1	(2.Al.)	(mgAll.)	isigalla	tumot/L :	(muold,)	(macti)
 -	22	,22	22	**************************************	**************************************	haran aran aran aran aran aran aran aran	17
(24)	13	29	103	7.5	(4) 6	4.30	101.2
1040	3.3	3 H	10.9	88	; # ## *	1.19	DALL
043	3.4	31	104	SPH	. 1421	4.96	183.3
7044	3.3	29	10.5	8.3	1.40 3	n (8)	[41] 4
1045	3.2	2.8	107	SPH	3 842 7	5,41	300 9
1046	3.1	2.9	10.2	8.6	139.9	5.72	181.8
704"	1.1	31	106	SPIL	140%	5.52	1404
1,40	3.3	27	109	16 (1	1420	5.31	F68.
OF.	3.3	28	103	MEH	141.3	ú.23	1029
16.90	3.2	29	103	9.4	141 4	5,95	1026

Courp 2: 512 mg kg die offen narouwe oormopredero 250 mg kg day of the withe ngwolen Osesp 3: 0024 mg kg, day of nge addustrie oorsoprede to 500 mg kg/dg/ of the selve algorithm Georp 3: 1535 mg/kg/day of the nationarie oorsoprede to 753 mg/kg/day of the active nigredient Clentral Dathology Results for Sey Legberroglebin Preparation - A 28-Day Dictary Study in Rata

Tobestoned Angray (Single) 49 to 1877 1884

Sex Male Dayes, Relative to Sun Dete-

1336				Streets Own Pha-			
mg kg sky Green I	HEEM	HEM LIP	ILT	AST	ALT	\$1:33	ALKP
		3		312 L r	1484	£9.)	14 (2.1
	32	- 32	33	22	55	22 .	72
7fml	None	Note	Norm	×;	i.s	: 9 ;	#2#
1996	lineae	None	None	SER	32	NPB ²	883
77063	None	None	None	8.1	33	7.9	24.7
164	Nouse	Nom	New	**	33	86	23.5
11.65	None	Nepe	Nexu	Q,C	3.5	3.2	181
74766	None	None	Noor	65	24	8.4	286
18/65	Time	Norma	Norm	SPH	25	8793	22.1
16936	Name	Netr	None	7.3	31	10.2	25.1
70,999	None	Neme	None		23	7.3	125
3050	Name	Northead	Nino		33	6.	196

Yes	5.6+lm	fyma	1 Residence	to Start	fres.

153%				three three three			
աբել հո	RILI	BUN	CREA	(\$6.1L	1RIG	OLIX :	33,
Group I	emzelle	emandi.e	(mg/dil.)	roug/dL)	empati.+	ongolla ;	1238.1
·	21	22	443	23	= .	=	
1441	012	11	#1 2 J	52	545	1415	2(1
6.62	649	ŋ	1) 25	61	45	92	6.1
7/63	er (#1	11	17.21	^}	304	(46)	6.1
11.02	41.19		15 EU	30	78	1800	640
1265	435	11	0.21	68	54	81	5.8
1.66	818	12	ri 22	**	92	102	63
1661	15 (19	12	14.22	85	116	101	6.1
1168	0.20	1 22	0.23	-\$6	47	92	6.5
*6960	iifa	11	o C	62	33	101	5.4
78,670	12 \$7	11	018	K3	65	91	61

Group I 512 marks the often moments correspond to 200 marks to other more important. Compt 1 1024 marks from entered more correspond to 200 marks to other more expendent. Group 1 1006 marks from the more expendent correspond to 200 marks to the more expendent from 1 1006 marks from the more expendent to 200 marks to the more engineers.

Convent Futhology Results for Sep Legistimoglobin Propusation - A 28-Day Dictary Stack in Rate

Individual America, concrete formitting form

Sex Male Days of Relative to Sun Date

1536				Olverno Clare Pho			
ing-karday Greize I	ALD	GLA)B	CAUC	uns	NA	K	۱٦,
	ig ville	12.11.1	(mg.dl.)	(क्रमुचीज	mmol4.5	cumol4.	(mesol),)
	22	22	22	::		Ann maria ann an Anna Anna an	33
*Cm	3.2	2 9	(0)3	? ¥	142.2	4.83	sat 7
1062	3.3	28	(0)	SEH	132.6	5.44	1022
7063	3.3	28	193	88	1421	5 (44	100.9
7064	3.3	2.7	10.5	ÇĶ	123	5.29	103.6
06	3.1	2.3	1618	89	[\$0]	5.21	Total
1066	3.0	3.1	808	8.6	10.9	3.97	103.5
1,v)	4.1	3.0	107	VPH	1406	5.00	101.6
Titox	3.4	24	79,7	88	131.8	-1.85	1003
1099	3.1	24	101	8.4	142.5	1.C	1843
1670	3.2	29	106	8.3	141.6	471	101.3

Courp 2: 542 mg kg, the offert outstake correspond to 250 mg kg, day of the active ingredient. Group 1: 302 trigs kg, day of the active significant. Group 1: 302 trigs kg, day of the active significant. Group 1: 1555 mg/kg, day of the active significant.

Claused Dathology Results for Sey Leghermoglobin Propuration - A 28-Day Dictary Study in Rata

Children Andrews From the Petrology Late

Sex Female - Depts) Reference to Stan Date

60			•	disease Over the			
mgaksasta Green i	11FAi	LIF	. ICT	Vat.	LIA	SIM	ALKP
28.4				471)	HALI	sU4.4	# 2.1
]-	22	33	33	22	2	2	72
3011	Some	Now	Niget :	'n	31	79	152
392	None	None	hong	56	26	58	(12
2013	Notes	None	None	78	25	6.	134
71)] 4	None	New	Nexa	*4	21	14.5	11.2
1085	Sone	Sep	Notes	66	21	۱۸:	§14
1646	None	None	tions	59	25	33.0	154
7017	Some	Name	None	69	23	x <	*31
1618	None	None	Nume	68K	24	ńâ	155
7019	Tracci	Note	Nove	SEH	21	NPH	3.40
7030	None	None	None	66	25	330	139

Sex Fociale Degras Relative to Start Date

ti l			,	Hymness Chem Ples			
mgdgadig Googi I	LIIM	HCN.	CREA	CROL	าหล	GLAX	TP
	ting vill.)	முத்தேர	(१४६८)	ामियुक्ता	साम्रहःसः (mg-d),r	egyb. (
	22	14	22	<u> </u>	<u> </u>		22
1(1)1	018	12	12 29	82	31	136	0.5
1012	048	1.3	0.26	**	31	116	67
7013	0.33	12	11.29	85	41	123	68
101.4	946	15	12.29	16	33	150	4.8
1015	04.	1.1	9.32	*1	41	125	6.3
*016	649	11	0.29	90	39	92	63
1011	4115	12	11.25	(A)	15	1105	6.0
1018	1116	12	11.20	85	30	124	65
1019	0.36	12	6.21	102	32	101	6.2
3020	41.59	"	11.24	60	4.0	118	5.0

Group 2, 512 mg/kg sign of the monoscop correspondence 250 mg/kg sidny of the active regordant.
Group 1, 1024 mg/kg/shy of the medicative correspondence 250 mg/kg sidny of the active regordant.
Group 1, 1256 mg/kg/shy of her medicative correspondence 2700 mg/kg/sidny of the active regordant.

Classial Puthology Results for Sey Leghemoglobin Preparation | A 28-Day Dietary Study in feets

Consistential Allera, Titlera, 1992/2009 Lata

Sex Semale Doyls) Relating to Stan Oate

D I	Observa Claim Pho										
mudigalay Group I	ALP	ALB GLOB	CALC	IPHS	NA	K	17.				
	1,327 छ।	12/11.1	(mgalia)	ւաբժեւ	nmed).:	(Arbann)	(marce), (
-	22	22	22	33 33	• • • • • • • • • • • • • • • • • • •		77				
7011	36 ;	20	105	7.3	119.4	4.64	182.6				
1012	3.2	£1)	10.	68	1408	115	1927				
011	3.8	3.0	108	7.3	139.4	430	105.5				
76) 4	1.1	31 3	164	66	141.6	4.21	105.2				
01.	3.5	: 8	9,9	68	1.938	111	1920				
047	3.4	29	Bet	* 1	138.5	4.45	101.2				
7017	3.3	2.	100*	70	140.9	5.14	1038				
*01 %	3.5	3.6	16-8	. 6	10.5	4.63	1930				
2010	3.3	2.9	10.5	NEIL	139.6	47)	102.0				
1020	3.3	2.7	103	6.6	140.2	4.62	1//2/6				

- 58 -

Course 2, 512 for English of the substance contemporalists 200 marks, day of the active translated Course 1, 1022 tracks, day of the active translates corresponds to 500 marks had be said to state angeolists Course 1, 1500 marks day of the active angeolists Course 1, 1500 marks day of the active angeolists corresponds to 750 marks play of the active angeolists of the active angeolists.

Chancal Puthology Results for Sep Leghemoglobin Preparation - A 28-Day Dectary Study in Rus

The Distriction of the American Control of the Section (Section 1)

Sex Formale - Doyler Retering to Stan Dute

512				demina Clum l'ka			
mukasko Grego 2	HEM	CIP	ICT	AST	ALI	SID	ALKP
				104.)	at/Li	(OL)	(1.3,)
<u>†</u> -	22	22	22	33	53 64	22	17
103i	None	Nuw	None	71	u	R.Z	97
1092	None	Note	None	78	22	86	:11
1033	None	None	None	78	2-	93	321
7034	Some	Neste	Norm	59	./5	R.3	415
1005	None	home	None	4.5	19	4.4	98
1036	None	None	None	58	24	6.3	1.35
7001	Nume	Some	None	83	32	7.1	100
2038	None	None	Note	761	31	83	127
1039	T) ave	Note	Neura	NFH	20	NTH	90
1040	Hone	Num	None	58	24	68	713

v	Formle	Discourse	Balabar		£2.44
341	Security	DESIGN	HU: OF IV.	D 2151	1.31

512	a shada barra ta abbarba barra a saasa			Olympia Cham Pks			
ma ka shi	BILI	HUM	CREA	CFRU.	TRICI	aux.	TF
Freign 1	l i						
	(mgv2.)	(Edga)	(REALISE,)	naga(dt.)	emg-dl.)	interdi.i	(文文社,)
	1102.141.7	This Car.	(1194-04.1	1 10 pc (14.7)	- mir carr	THE WILL	134,544,1
	e egge		11.54			~	
	24	44			<u></u>		
2038	0.26	101	0.24	u;	29	91	6.8
1032	a 19	ŋ	0,25	13.	4*	k/>	69
1033	(1.38	D	0.26	7	2:	131	71
1034	uzi	11	0.26	u:	11	100	3.4
1033	ote	11	0.28	78	30	95	9.1
1.35	0.20	12	++ 2%	91	14	9*	6*
1037	(0.20)	9	0.22	89	51	95	4.1
1038	913	- 11	9.27	87	12	117	6.4
7039	0.21	10	ti 25	137	47	138	6.3
7040	31 19	14	(1.28	86	12	106	* r,

Over 2.512 mg/kg dry of ten nibration corresponders. To snig/kg, dry of the active singulated.

Comp 7. 1074 mg/kg/dry of the nibration extraordinals to 90 mg/kg/dry of the active singulated (Sonip 1.1500 mg/kg/dry of the active singulated (Sonip 1.1500 mg/kg/dry of the active singulated

Clanical Enthology Results for Sep Leghermoglobin Preparation - A 28-Day Dectary Study in Rata

[Treffers field Assembly Ferm on Consultable Conf.

Sex Sexuale Degras Reference to Stan Oale

512	Olympia Claim Pka										
marka skiy	ALI	GLOB	CALC	UFHS	NA	K.	۲٦,				
Group 2	+ ታ ኒያኒ ፣	Fg.VII. I	(ergr. (ff.)	t.lb:4mt	enmod L:	cantiol ⁱ Ls	(mesos-3.)				
]	22	22	22	77	TO STATE OF THE ST	3	7.2				
7031	3.7	11	ti i		1403	4.724	101.2				
1032	3.5	3.4	Un	8.3	141.0	5 18	90,7				
7033	3.9	3.2	11.0	8.3	139.9	176	99.6				
26:34	42	3.2	11.2	H -2	140 (4.78	90 n				
1735	3.5	29	103	2.5	188	1,23	\$83.3				
1036	3.2	3.6	11.2	8.3	140 7	1.2	. 191.2				
7037	1,5	2.0	1116	.	140.8	4.68	101				
0.38	3.5	2.9	104	7.1	(38.9	5.09	1802.9				
1039	3.5	28	11.2	NEH	1-51- 4	1.K2	183.6				
*040	3.5	3.5	10.8	6.1	140.2	3.99	101.6				

Courp 2: S12 mg hg dim often addition contributation. No mg hg stoy of the natur ingrothers. Design 7: 1024 mg hg day of the addition contributable 900 mg hg tips of the additing against a Formy 8: 1736 mg/hg day of the additions contributed to 750 mg/hg tidy of the active ingredient. Clinical Puthology Results for Soy Legicinoglobin Preparation | A 28-Day Ucetany Study in Isaa

interined Access the a Participal Late

Sex Female Degras Reference to Stan Date

1023				Olympia Chim Plac			
mg-kastoj Gorup J	FIEM	I.IP	t:T	AST	ALT	SCH	ALKP
				iUU	sti Li	(0),1	31 A.1
	22	22	23	3	70% 1000	22 1	7.7
16/61	Sone	Som	Nonw	73	3.1	R.	3.11
962	None	Scotts	Personal Property of the Personal Property of	7.5	36	ላ የ	3.52
1063	None	Nume	None	67	25	8.1	302
71 (54	Nome	None	None	55) †	1.6	(-1
2065	Now	Nem	Soon	V.,	29	8.9	913
1066	Nume	None	None	163	20	0.1	107
1661	Norm	Norm	Nimw	16.1	25	7.0	151
1058	None	Norm	\$60000	(4)	> >	7.3	(U)
70,99	Mane	None	None	(4)	23	9.7	131
((A)	Notes	Té coma	None	665	23	**	136

Ser Female - Dayto Relative to Start Date

1024				thrown Chin Plea			
uig-kardin Greup J	BILJ	147.57	ERFA.	CENT	rud	anx	IF
	rmacell.)	1102-4.1	(ಗ್ರಾ/ಟಿ.)	ragálta	આદુ:તી.⊁	+Lb-2inc	(東)北(
	11	22		<u> </u>	<u>=</u>		22
'irşt	(1.2)	[]	D21	96	52	(8)	65
1062	a 19	13	0.25	~ 1	21	90	6.B
1/53	0.17	16	11 21	1)6	÷ı	1,61	- 3
1415.3	a fy	12	11 13	ROS	Q.	367	6.8
1065	0.20	- 11	to 26	82	66	127	69
1066	0.25	14	0.27	90	48	\$15	61
2057	11 🗱	13	14.21	106	35	\$11	6.1
11.00	a 🚉	10	(4.28)	117	72	96	7.2
1049	817	12	er 208	[6]	47	981	56
1060	(1.29)	- 11	6(2)	129	42	\$113	56

1081 0 20 11 12 Compt on other abstracts correspond to 20 mg/dg day other kind ingestions from the All Market ingestions of the All

- n] -

Claused Pathology Results for Sey Leghemoglobin Preparation | A 28-Day Dectary Stack in first

Indication Animal time as twice say Cara

Sex Female - Hopest Relating to Stan Date

1024	Olemps Chem Phs										
mg ka day Gregori	ALB	ALB GLOB	CALC	tPHS	NA	к	t 3.				
1	12 VSL 1	اللاعا	(१८४१:वी.)	।श्रष्ट्रची.।	aunol:1.:	cumoPl, r	(mre%).)				
<u> </u> -	22	32	***	>5 4.7	~	~~	7.7				
1081	3.6	2.9	(0.5	- 3	1397	4.52	£00.3				
1082	3.0	3.1	10:	10	1403	1,00	102.4				
1063	3.8	3.5	H.A.	- 8	1495	1.58	100.9				
2054	36	12	11.3	5.5	140.1	4.08	1001				
2055	3.8	3.1	link	10	1009	179	58L1				
166	3.6	3 0	tt.i	8.1	140.0	159	‡iiXi 4				
165	1.1	29	tov	* 4	139 *	4.51	361.2				
0.88	3.0	3.2	11.5	- 4	130 3	4 80	\$000				
059	3.5	3.1	t I a	8.2	1012	480	193.3				
1060	3.6	3.0	11.2	*6	1 10 5	5 (12)	99.7				

- 62 -

Coup 2: 512 the highest often industrie contemporation 250 the highest of the active trigorders. Therep 3: 1021 the highest often industrie corresponds to 500 the highest of the belief algorithms. Cartap 3: 1350 they highest of the industrie corresponds to 5700 they highest of the active distribution of the active Classical Probelogy Residus for Sey Legistanoglobia Preparation - A 28-Day Dictary Study in four

Inductional Angelia come in February Lines.

Sex Female Doyler Relative to Stan Date

1536	thrones Them Plan									
mgdstakn Grego I	HEM	r.ps	rer	AST	ALT.	21:04	ALKP			
				(N4.)	49 L)	39 L)	(U4)			
	12	22	22	33	59	8	77			
10773	None	None	Rinn	76	24 .	7 (88			
1002	None	State	Petros	69	Al .	K.	1 18			
1073	Notes	None	Norac	7.\$	32	12.7	78			
7074	None	None	Norw	76.2);	89	78			
1075	Note	Netw	None	rit	28	8.2	315			
1076	None	None	None	57	24	114	934			
71977	None	None	Nume	60	2-	RA :	1310			
1978	Sone	34pte	Nome	56	20	7.5	194			
3079	Name	Note	None	65	2"	157	349			
7(483)	None	Sime	Ninar	267	23	10.2	117			

Sex Fonale Degras Relative to Statt Date

1536	Olympian Cham Pha									
արելեր ։	Lus	BLN	C'REA	CML	เหนด	aux :	11,			
Group I	(mg>£.)	118Z11.0	(छक्षी.)	ामµ'dL)	(Illegin)	amgadi.)	(xxi).			
	<u>::</u> :	±2	<u></u>	₫ .	<u></u> -	<u> </u>	2."			
311,2	4) <u>*</u> [16	11	0.25	k)	29	89	6.1			
7072	810	12	0.26	79	29	195	66			
7073	24. 2 01	12	0.32	138	44	100	- 3			
7074	649	13	0.33	100	31	1.51	- 2			
1075	4.22	13	0.26	120	345	[(4)	6.5			
7076	9-214	11	0.25	6}	27	183	4.1			
7021	4119	10	0.25	121	52	105	6.6			
1778	9(1)	1.3	0.26	\$50	31	1900	6.3			
1079	0.22	13	0 B	100	35	130	کر چ ا			
1080	a 2a - 3	14	0.32	(La	41	123	5.5			

Group 2, 512 mg/kg day of four influence correspondence. For ingelig, day of the known agreed and Comp. 1, 1024 mg/kg/chy of the influence correspondence. Which ingelig day of the including agreedance Correspondence. The ingelig day of the active ingredience correspondence. The ingelig day of the active ingredience.

Christal Pathology Results for Soy Leghemoglobin Preparation: A 28-Day Dictary Study in Rata

Individue Backet (fig., a) Saffring (ata

Sex: Female Day(a) Relaine to Sun Due

1536	Ohtmas Chen Flor									
make day	31.8	GLAG	CALC	IPH5	NA NA	K	.1.			
Charge 4	:					:				
	cgoff. r	sg.(वी.)	+, 11cgm+	195 9 .18.1	(1900 (V).)	chepol/Li	(क्स्सल्स्)। ।			
l	22	12	22	22	23	22	11			
7071	36	29	105	69	1303	5 21	1028			
31.02	33 -	31	105	δŸ	(38.0)	518	101.8			
7603	+1	3.2	113	7.3	3 70 9	4.66	101 3			
7074	39	3.3 :	108	6.3	341.2	429	1029			
2675	10	3.0	113	69	1.00	1 37	1013			
7076	33	28	106	7.6	1.301.3	4.99	163.3			
4650	30	36 .	111	246	1,59.8	5.23	99 %			
1078	33	3 0	10.9	86	1417	4.61	103.0			
2079	3.5	30 :	103 -	5-	1.79	4.54	1024			
1090	3.6	29	100	65	140.2	4.39	1028			

Pemp 2, 112 mpkg my afree enheuses compensh in 250 mg/kg/day af the active semalast. Outp. 1. 102 mg/kg/day af test adolatice compensh in 500 mg/kg/day af the active age obted. Doug 4, 1550 mg/kg/day af test adolatice compensh in 750 mg/kg/day af the active age obted.

- t)-i -

Chrisid Pathology Rosalis for Soy Leghemoglobin Preparation | A 28-Day Dietary Study in Rata

Industrious modes, liste to Part 1009 parts

Sex: Male Days is Relative to Start Date

4)				avoltA H.A.S			
tog-kgrday	QUAL.	4504.	CLAR	1.VOL	şıH	SU	UGLC
ticom I	i						
				ant.i			स्थान्यस्य
	22	22	22	22	::	크	· <u></u>
*003	Luita :	Yelkin	Clear	2.4	6.0	1.072	NEGATIVE
) (4) (2)	E.ight	Yellow	tiazy	*2	6.0	1,1029	NEGATIVE
7003	Coelit	Yellon	(Bear	26	6.5	1.024	NEGATIVE
16834	Light	Yellow	Liter	60	6.5	1.027	NEGATIVE
7005	(.igh	Yeikow	- Set	168	7.0	1.013	SEGATIVE
3006	Light	Yeikm	Clear	12	6	1106	KEGATIVE
2000	i.igln	't ellen	Liteer	18.2	~ 6	1.016	NEGATIVE
7008	i.igla	Yellow	(Team	149	6.5	1.016	NEGATIVE
2009	Medann	i elkov	Hazx	3.6	6.5	1.043	NEGATIVE
7010	Light	Yeiker	1, Tan	Terro -	7 p :	1100	NEGATIVE

Charp 2, 512 mickie day of leat estatence comequate to 201 mickigolay of the active expodest Croup 7, 1023 mickigolay of the substance comequate to 400 mickigolay of the active expodest Croup 4, 1559 mickigolay of feet substance comequate to 450 mickigolay of the active expodest

Climical Pathology Results for Soy Legitemoglobin Preparation - A 28-Day Dietary Study in Rain

Individual masses, little of Early Logs Salis

Sex: Male | Duyer) Relative to Start Date

44		แรก	ALLAS		Obsaces Ches Phi	
nighterally mg/dg/day	K£7	CIBL	HLD	198+	UMTP	
` J	mp ill.			(野野)建。	ongd),	
ŀ	22	22	. 2	٠ <u>ي</u>	22	
*000	TRACE	NEGATIVE	NEGATIVE	16	194	
1002	TRACE	NEGATIVE	NEGATIVE	0.2	113	
1003	15	NEGATIVE	NEGATIVE	0.2	84	
2001	15	NEGATIVE	NEGATIVE	0.2	85	
10.5	NEGATIVE	SEGATIVE	LARGE	0.2	46	
3006	15	SEGATIVE	NEOATIVE	0.2	129	
· 00	NEGATIVE	NEGATIVE	TRACE	0.2	65	
1008	TRACE	SEGATIVE	LARGE	0.2	40	
1009	15	NEGATIVE	TRACE	0.2	175	
2010	SUIATIVE	NEGATIVE	NEGATIVE	62	. 18	

Durip 2, 512 makin dip officif substitute extraposable to 250 makin high at the active approduct Comp 3, 1021 makin sign of too adoptive correspondent 500 makin sign of the earlier appoints Crosp 4, 1550 makin sign of too adoptive correspondent 550 makin sign of the earlier sar observe Chinaid Pathology Residu (ce Soy Legisemoglobia Preparation - A 28-Day Dietary Study in Reta

Codavident books, time at Fatt 1-22 buts

Sex: Male Day or Relaine to Start Date

512				webA 11.33			
me be day	QUAL.	13.4	PA.T.	UNSA.	pH	%U	UGLZ
Georgi 2							
				(III)			
	22	22 .	≃ ;	22	: :=	**	22
1021	Light	Yeikw	Hazv	1.8	6.6	1.042	MEGATIVE
1022	tgtn	Yellow	4 younty	9.6	1 7.0	£ 1/24	NEGATIVE
1023	Loght	Yelkim	Hazy	60	6.1	\$ 1843	SEGATIVE
7624	Light	Yellow	Clear	4.0	6.0	1.052	NEGATIVE
7025	Light	Yelkov	Con	154	7.0	1.045	SHOATIVE
1426	Light	i citra	(Aesa	290	6.5	1.011	NEGATIVE
1002	Light	Yellon	Clea	158	6.5	010	NEGATIVE
70028	Light	Yelkow	Com	0.1	QNS	QNS	088
7029	Light	Yelkor	Hazr	26.0	7.0	1.013	NEGATIVE
1000	Light	Yeikow	(Can	4 16	· 2:13	£ 040	NEGATIVE

Charp 2. M2 media dry affert nitramenes amagente in 290 mediality of the source norodan (Jaup 2. f071 mg kip dry of for automote correspondent for mg kip dry of the other nigrosses (Laup 1. 1826 mg kip dry of for automote correspondent in "O medig thy of the other nagendent

Christial Pathology Results for Soy Leghemogloban Preparation - A 28-Day Dietary Study in Ruts

Indication makes this or Extension between

Sex: Male Duy 1) Relatine to Start Date

5)2		nyak	ADAS		Obmous Chem Pla
mg/kg/day	KET	ein.	nrn	UR+	CMTF
:Iomp 2	emyall.	0 00 Con 100		4811/4 3 .3	c.ttegm)
ŀ	22	<u>-</u>		**	
1(0)	TRACE	NEGATIVE	FRACE	02	123
11427	TRACE	NEGATIVE	LARGE	0.2	110
7023	15	NEGATIVE	NEDATIVE	0.2	3515
7004	NEGATIVE	NEGATIVE	NEGATIVE	0.2	250
2029	NEGATIVE	NEGATIVE	NEGATIVE	44.2	133
3426	NEGATIVE	NEGATIVE.	TRACE	44.2	18
200	TRACE	SEGATIVE	NEGATIVE	12,2	18
70728	QNS	083	ONS	QNS	1,250
1029	TRAUE	NEGATIVE	NEGRATIVE	0.2	24
7030	TRACE	NEGIATIVE	SEGATIVE	1+2	185

Chaip 2. M2 mg/kg day of that sebetance con repeated so 290 mg/kg/day of the active suspedient. Chaip 3: 1024 mg/kg/day of the advisance corresponds to 500 mg/kg/day of the same neglected. Chaip 3: 1550 mg/kg/day of the submission corresponds to 750 mg/kg/day of the same neglected. Chaical Puthology Results for Sey Leghemoglobin Prepaintion - A 28-Day Dietary Study in Rata

TROUGHUAD BROKES - 1966 to Party Poly years

Sex: Made | Dini in Relative to Start Date

1921				uvoPA4LAS			
mg ku day	QUAL.	COL	CLAR	CWA	Hq	50	CARC
tiroup 3	Ì			वार्त्तः :			enrp/d[
1	22	<u> 22</u>	22	22	22	<u></u>	. 21
1041	Luli:	Yeikw	Close	24.4	- (₁	£ 011	NEGATIVE
5142	Light	Yellow	Gea	9.8	6.5	3.024	SEGATIVE
7643	Could	Ye)ken	Tear	4.2	60	7 (42	MEGATIVE
19844	Light	Yellow	Clea	19.0	6.5	1 017	NEGATIVE
7645	Light	Yelkow	Haey	72.6	7.0	3 (42	NEGATIVE
7046	Light 0	Proon P	Charly P	36 9	65.0	3.064.8	NEGATIVE 10
*64"	Light	tellen	l, lea	(3)6	n a	10,022	NEGATIVE
7048	Light	i elkor	Hazy	11.0	6.5	1.412%	NEGATIVE
7049	4. uelit	Yellon	Litea	* 12	6.5	1.023	NEGATIVE
1036	Light	Yelkor	(Tose	9p :	- 0	1+424	SECATIVE

USC Freed consensummer observed.)

Comp.2. MC residencies of the administration companies at 20 may ben'ny of the source separates. Comp.3. 1071 may be of the source separates at 500 may be given a set of the source separates at 500 may be given to the separate set of the separate set

Chronal Pathology Results for Sey Leghernegletan Preparation A 28-Day Dietary Smity in Rata

Individual delixare com as Earlicency for i

Sex: Male Duyes Relaine to Start Due

3023		acol-	AHAS	3.0	thraces Olean Plu
mgikarday tinoso 3	KE7	CHA.	บเบ	1/80	ENTP
, j	ւրթյվք,.			6838 TA # .)	ranged), s
ŀ	<u>==</u>	· <u>-</u>	: 22 5	22	22
7011	TRACE !	NEGATIVE	IRACE	02	34
1142	TRACE	SEGATIVE	SEGATIVE	0.2	61
7043	TRACE	NEGATIVE	SMALL.	0.2	230
7044	NEGATIYE	NEGATIVE	SMALL	0.2	103
7045	TRACE	SECATIVE	ME OURATE	0.2	69
ાતક	15 0	SMALL	LARGE P	10.0	200
2045	TRACE	NEGATIVE	NEGATIVE	0,2	159
704R	15	NEGATIVE	MODERATE	0.3	106
7049	TRACE	NEGATIVE	TRACE	0.2	98
7050	TRACE	NEGATIVE	MODERATE	6(2)	93

^{1 (}SC Freat contamination observed.)

Thought No make the office substance conspectable (29) make they of the advect inspectant (2015) 3 (1977) p. (1977) advect inspectant (2015) 3 (1977) p. (1977) advect agreement (2015) p. (1977) p.

Chancal Pathology Results for See Leghemoglobar Preparation - A 28-Day Dietary Stady in Rata

Computeryor business their or Entlichage Conta-

Sex: Make | Dung so Reliance to Start Date

15,85	avol'A H.AS									
mg/kg/rhiy tironp 4	QUAL.	201,	CLAR	1.Ve4.	Hq	50	COIX			
·				unt.			sm#4ll.i			
ł	22	22 :	***	22		22	22			
1,61	Liula	Yeikin	Hazy	158	6.5 į	1.020	NEGATIVE			
1062	Light	Yellow	Clea	119	0.5	1.019	NEGATIVE			
7063	i inglit	Telking	107cm	10.2	6.5	1.024	MEGATIVE			
2064	1.telp	Yellow	Clea	31 0	- ₁₎ {	1.011	NEGATIVE			
7065	Light	Yeikor	(Near	1697	h tr	3 (1) 8	SEGATIVE			
1066	Light	reikm	Huzy	15.4	20	1.0[*	MEGATIVE			
1067	Medium "	Yellow P	Unicapty 27	9.6 1	7,6 € ∮	1.022 0	NEGATIVE #			
10/98	tifgit, f	Yelkov	Char	128	6 5	1 (46	SEGATIVE			
1069	Light	Yelkor	Clear	1 P 🤚	60	7.66.6	NEGATIVE			
7076	Light	Yeikw	Hiney	196	7 p	19015	NEOATIVE			

T ISC Feed contamination observed ().
Doug 2, 312 make the office abstence composite to 29 make, they of the action against the course (1003 mg kg) they of the action against correspondent for mg kg) they of the action against correspondent for mg kg) of the other against a correspondent from the kg) and of the interespondent from the mg kg) of the interespondent from the first the consideration of the co

Christoff Pathology Results for Sey Leighermoglobin Preparation - A 28-Day Dietary Study in Rafa

Individual brins, little of table long bats

Sex Male Buyin Reliancito Stati Dute

1536		uvobā ILAS								
mg barday [KE7	L'1856.	ULD	URO	CMP					
tleonb ≰	ւտց մե, չ			(程序)建计	·brym+					
	22	22	<u>.</u> == *	± †	=					
*961	TRACE	MEGATIVE	SMALL.	0.7	7.7					
3863	NEOATIVE	NEGRATIVE	NEGATIVE	0.2	k.;					
*967	15	NEGATIVE	NEGATIVE	0.2	120					
1664	NEGATIVE	NEGATIVE	MODERATE	0.2	15					
1044	NEGRATIVE	NEGATIVE	SMALL.	6.7	5.3					
1066	KDMINH	NEGATIVE	LARGE	4:2	97					
1087	45 (0.1)	NEOATIVE #	LARGE P	342 P	148					
2048	TRACE	NEGATIVE	SMALL	62	92					
7069	NEGATIVE	NEGATIVE	NEGATIVE	0.2	380					
7076	TRACE	SECATIVE	LAROE	66.2	55					

³ ISC Feoil consummation of some of 1 Group 2, 512 majority of test substance computed to 200 majority of the source supposites Group 3, 1073 majority of test substance corresponds to 300 majority of the same agradient Group 1, 1550 majority of the substance corresponds to 300 majority of of the same agradient

Chancal Pathology Results for Soy Leghemogloban Preparation - A 28-Day Dietury Saidy in Rula

Podskiewa Mickey Little in Early Pozy Data

Sex Female Davin Relative to Start Date

e	ovol/A R. AS									
mprigadity	QUM.	CNOL .	CLAR	UYGL	pil	50	COLC			
Scoup I				usta			emgedl.a			
÷	22	ż ·	. 22	22	22	<u></u>	***			
7011	វ.រដ្ឋដ	Yeskow	Сюн	0.5	6.0	1.1(4) 11	NEGATIVE			
1012	l.ieln	Yelkon	Clea	12	6.0	1 039	NEGATIVE			
7013	1.ugle	Yelkon	Hutv	1.6	6.5	1.025	NEGATIVE			
3014	Light	reliew	Harv	3.6	~ ()	1.038	NEGATIVE			
2015	Ligh	Yelkor	िरम	38	6.0	1 (417	NEGATIVE			
2016	Light	Yelkra	(Jen	18.2	6.5	1.012	NEGATIVE			
2017	Light	'i ellon	1.Text	154	0.5	1.040	NEGATIVE			
70JR	Light	Yelkor	िंदश	ù 9	65	1.058	NEGATIVE			
2019	Light	Yellow	Clear	15.0	6.0	1 013	NEGATIVE			
7026	Medium	Yeikow	Cloudy	8.6	*0	1.025	NEGATIVE			

¹ ISC. Specific alexity result is >1 IBO Turp 2 SI make the office substance are necessed to 29 mach publy rithe solve apprehen-tory 1 1021 make the office advantage corresponds to 50 mach publy of the time apprehen-tory 1 1356 make this office advantage corresponds to 50 mach publy of the time real select

Climical Pathology Results for Sey Leghernoglobin Preparation - A 28-Day Dictary Study in Rata

Individual biotics, title in hith contracts

Sex: Femalo - Dayra) Relative to Stan Date

i 1		lis e	AHAS		Physical Chees Plu	
աերքարհ	KE7	uun.	PLD	URLE	CMTP	
ւնտար 1	etheym)	the day of the second		(81°a⊈.)	emg-sD.	
	22	7.	. <u></u> .	*	22	
7011	NEGATIVE	SMALL	NEGATIVE	92	127	
5812	NEGATIVE	NEGATIVE	NEGATIVE	6.2	34	
स्थान	NEGATIVE	SEGATIVE	TRACE	62	31	
391.1	NUGATIVE	NEGATIVE	SMAIA	442	3.7	
7045	NEGATIVE	NEGATIVE	SEGATIVE	617	417	
140	NDMATIVE	NEGATIVE	MIGHATIVE	62	- 11	
1997	NEGATIVE	NEGATINE	SEGATIVE	942	. 9	
7018	NEGATIVE	NEGATIVE	LARGE	6.2	69	
7919	NEGATIVE	NEGATIVE	NEADATIVE	02	22	
3020	NEGATIVE	SEGNITVE	MODERATE	62	38	

Outp. 2. N.2 make dry offerd substance excepted to 250 makely of the after appelled. Coup. 3. 1021 mg. hg. dry offerd advants correspond to 200 mg. hg. dry of this stary appelled. Coup. 3. 1550 mg. kg. dry offer advants excepted to 250 mg. hg. dry of this stary substance excepted to 250 mg. kg. dry of this stary substance.

Chancel Pathology Results for Soy Leghemoglobin Preparation: A 28-Day Dietary Shidy in Rata

Consultant Books, title at Esticators Satis

Sex: Female - Daviso Relative to Start Date

512	ovoPATLAS									
me progra	QUAL.	CD1.	CLAH	CYNA	На	3KJ	COLC			
throup 2		•		onta			பந்திக			
1	22	<u>r</u> ,	**	22	22	**	22			
1001	Luit	Yeilow	Сай	5.8	6.0	1.031	NEGATIVE			
302	Light	Yellow	Hazy	124	* B	3.013	NEGATIVE			
7613.3	ર જાણ	Yellow	Chain	10	6.0	1.076	MEGATIVE			
7694	Light	Yellow	Hazy	76	0.5	1.029	NEGATIVE			
2005	tigle	Yelkor) Total	11.2	n B	100	SBUATIVE			
7036	Light	Yeikm	1.Toan	168	6.5	1.011	NEGATIVE			
1030	ំនៅព - នៅព្រះ	Yelkin	l. loa	2.8	p. 0	1.040	NEGATIVE			
7038	Madiani	Yellow	Harv	16	6.6	1 (15)	NEGATIVE			
2039	i.uel#	Y olker	Clea	1.0	6.0	1.036	NEGATIVE			
1040	Light .	Yolkow	Пен	30	5.5	1.062	NEGATIVE			

Charp 2, 212 macha chy of task mistelman currasposide de 220 maplighty of the notice mayorisate (Coup 7, 1075 maplighty) of the native mayorisate (Coup 7, 1075 maplighty) of the native mayorisate (Coup 1, 1250 maplighty) of the native mayorisate (Coup 1, 1250 maplighty) of the native mayorisate

Chemist Pathology Results for Soy Leighermoglobin Preparation: A 28-Day Dietary Study in Rata

forthwarest material field as Farthway Data

Sex: Female | Dayto Relative to Start Date

532		lovel	AILAS		- Ohmeur Oben Phi	
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1(હ્ય	NEGATIVE	NEGATIVE	MODERATE	0.2	29,	
7039	NEGATIVE	NEGATIVE	NEGATIVE	62	16	
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Charp 2, 312 ma/a print of the substance corresponds to 250 ma/a, only of the notice associated (Courp 2, 1073 mg/a, of the notice associated (Courp 2, 1073 mg/a, of the notice associated (Courp 2, 1756 mg/

Clinical Duthilogy Results for Soy Leghemoglobin Prepaintion - A 28-Day Dietary Study in Rein

Comparishment tomorrows of the analysis to a separation

Sex: Female - Dayto Relative to Start Date

1921				uvol:A H.A.S			
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7053	1.celd	Yelkon	1 Tompty	8.0	7.0	\$1021	MEGATIVE
*054	Ligito	i cikm	.Teu	tur	p ts	1.017	NEGATIVE
7055	Light	Yeskow	Gen	3.0	n 5	Urdo	NEGATIVE
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1000	3-Sedium **	Ctrown 57	l'intied P	4,0 0 -	"50	1.028 0	NEGATIVE #
7058	Medium	Yelkm	1 Syenty	• 10	7.0	1.022	NEGATIVE
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^{1 1897} Fread constantinuosis observed.)

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Clement Puthology Results for Soy Leghemegloban Preparation | A 28-Day Dietary Study in Rata

Individual busines semi- 4 Problems Sata

Sex: Femile Dayno Relaine to Start Date

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1053	TRACE	NEGATIVE	LARGE	02	31
2084	NEGATIVE	MEGATIVE	NEGATIVE	6.2	Ð
(155	NEGATIVE	NEGATIVE	SEJATIVE	6.2	40
1056	NEGATIVE	NEGATIVE	NEGATIVE	0.3	20
ાહક	TRACE #	SMALL 0	LARGE #	9,2 10	56
7058	NEGATIVE	NEWATIVE	LARGE	62	32
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^{- 1 (}SC Freal Contamination observed.) Outpp 2 312 mg/kg/day of list addressed compagnation 20 mg/kg/day of the active appeleas Outpp 3 (62) mg/kg/day of ker addressed compagnation for mg/kg/day of the active appoints Outpp 3 (126) mg/kg/day of their addressed contamination of mg/kg/day of the active appoints

Chancel Pathology Results for Sey Leghemoglobin Preparation A 28-Day Dietary Stuch in Rata

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*11*3	₹. eg8tt	Yelkon	C7ear	50	6.0	1 026	SEGATIVE
7074	Light	Yellow	Clen	2.6	6.0	1.046	NEGATIVE
7075	Light	Yokm	1. Syst	12.6	6.0	\$10[4	SEGATIVE
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Christal Pathology Results for Soy Leghemoglobia Preputation A 28-Day Dietary Saich, in Reta

Computation and any other of Employage Data

Sex: Female - Dayto) Relative to Start Date

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mg karday	K£7	uin.	PLD	URti	UMT
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7071	NEGATIVE "	MEGATIVE P	LARGE P	62 P	-1-
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1013	NEGATIVE	NEGATIVE	TRACE	0.2	-12
1914	NEGATIVE	NEGATIVE	AR CHERTIE	0.2	46
1915	NEGATIVE	NEGATINE	SMALL	0.2	15
976	NEGATIVE	SEGATIVE	NEGATIVE	0.2	59
2652.2	NEGATIVE	NEOATIVE	LARGE	0,2	38
7078	NEGATIVE	NEGRATIVE	(.ARGE	0.2	15
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Chineil Pathology Results for Soy Leghermoglobin Preparation —A 28-Day Dietary Study in Rata

maint has marked of the experience, but s

Sex. Male ... Day(a) Relative to Start Unite

k)				Umne Ma	ernseap k			
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Clanical Pathology Results for Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rata

Summations observed Classical Verbriery Entw

Sex Male Day(s) Relative to Start Oute

512	[Grine M	44(II)ACII)PH			
mg kgidav. Greup 2	EPIT	UMBC	URIN	NCRY	MICR	SPER	KEŞI	MEC
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70:26				Few	Feu	Few		
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7⊅2K	ONS				1		\$:
76)29	Fee			Few	Fen	Few		
7030	F 476		-	Frw	Fent	FGM	-	

Chiep 2, 512 highly dry officer substance correspondents 250 mighly dry of the autocoappolice. Chiep 4, 1072 mighly dry of the substance correspondents (30 mighly dry of the autocoappolice) (1755 mighly dry of the autocoappolice).

Clinical Pathology Results for Soy Leghemoglobar Preparation A 28-Day Dictory Study in Rata

indistings named Clinical Participal Late

Sex. Male. Day(s) Relative to Start Date

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mg-Ag-dav Græp 3	EITT	UWBC	URBC	NCRY	MICR	SPER	KEPI	MUC
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7043	Few	Feb		i cu	Feu	Feu		_
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-71547		! .	-		Feu	Feu		
7848	Few	Fen		Mod	Mod	Mod	-	-
7649	Few			Few	Few	Few		
7050	Fow			Few	few	Feu	_	-

Crosp 2, 512 each gray of fed substance corresponds to 120 may be thy of the active agreebest. Trough 1,002 may be of fed substance corresponds to 1900 may be they of the active agreebest through 1,003 may be the active agreebest through 1,003 may be the active agreebest programment.

Chinical Pathology Results for Soy Legherneglobin Preparation: A 28-Day Dictory Study in Rata

Introduct Shired Clinical Party Lady Late

Sex. Male Day(s) Relative to Start Date

153n				Cime M	er () Ne () tyc	:		
mg-kgrdav Greep 4	EPT	towne	URBC	MORY	SHCR	SPER	KEPI	MUC
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706K		-		-	Few	Few		
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¹³⁵⁰ unine belom recommended volume!

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Clinical Pathology Results for Soy Eighemoglobin Preparation A 28-Day Dectiny Study in Rata

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Sex Female Dav(s) Relative to Start Date

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LISC terms below recommended volumed

Clanical Pathology Results for Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rain

Individual America Climater Tattoring Lark

Sex Female Dav(s) Relative to Start Date

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mg kgiday Sipsup Z	EPIT	CAVBC	CRAIT	NRY	MICR	SPER	REPI	<u>ላብ</u> .ሮ
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2035	Few	Few		Few	Mod			
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7038	Few	,		Mod	Mod		, ,	
7039			-	Few	Few			
20340	Few			Fen	Few			

FISC terms below recommended volume)

taurp 2, 51.2 mg/ka/mg afters addition contrapersts at 250 mg/ka/mg/after angelocia. Chuip 3, 1024 mg/ka/mg, ofteis adintaree contripersts to fast mat laying of the aditio and olient Chuip 4, 1534 mg/kg/mg, afteir advisance contripersts to ¹⁰0 mg/kg/mg/d the aditio and place

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Christial Pathology Results for Soy Leghemoglobia Preparation | A 28-Day Dietary Study in Rata

individual house clini at latering hara

Sex Female Davis) Relative to Start Date

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me ka day Gurup s	EPIT	CONTRC	रस्रक्षा	WRY	MICR	SPER	REPI	λ#IX*
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7036	Few			Few	Few.	-	-	-
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Clinical Pathology Results for Soy Leghemogloban Preparation: A 28-Day Dietary Saidy in Rata

markathan Americal Classical Patterlands Latin

Sex Female Dov(x) Relative to Start Date

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7078	Few			Feu	Feu			
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7080	Few			Fen	Few			

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APPENDIX O: ANIMAL NUMBERS, DOSE GROUPS, AND FATES1

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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

Removal Removal Removal Time Removal Pathology Slot Animal Cage Week Date Time Symptom Group Dose Level Sex Day Reason 0 mg/kg/day Male 7001 1 29 27/10/16 6:50 Term Term 7002 1 29 27/10/16 6:51 Term Term 7003 2 29 27/10/16 6:51 Term Term 7004 2 29 27/10/16 6:51 Term Term 29 27/10/16 Term 7005 3 6:52 Term 7006 3 29 27/10/16 6:52 Term Term 27/10/16 6:52 7007 29 Term Term 7008 4 29 27/10/16 6:53 Term Term 7009 5 29 27/10/16 6:53 Term Term 7010 5 29 27/10/16 6:53 Term Term 0 mg/kg/day Female 7011 6 30 28/10/16 6:50 Term Term 6 30 28/10/16 6:50 Term 7012 Term 7 28/10/16 7013 30 6:50 Term Term 7 7014 30 28/10/16 6:51 Term Term 7015 8 30 28/10/16 6:51 Term Term 30 28/10/16 6:51 Term 7016 8 Term 7017 9 30 28/10/16 6:52 Term Term 7018 9 30 28/10/16 6:52 Term Term 7019 10 30 28/10/16 6:53 Term Term 7020 10 30 28/10/16 6:53 Term Term 2 512 mg/kg/day Male 7021 11 29 27/10/16 6:56 Term Term 7022 11 29 27/10/16 6:57 Term Term 12 27/10/16 6:57 Term 7023 29 Term 12 29 Term 7024 27/10/16 6:57 Term 7025 13 29 27/10/16 6:58 Term Term 7026 13 29 27/10/16 6:58 Term Term 7027 14 29 27/10/16 6:59 Term Term 7028 14 29 27/10/16 6:59 Term Term 7029 15 29 27/10/16 6:59 Term Term

Individual Animal Fates

PSL Study Number 43166 A 28-Day Dietary Study in Rats

Removal Removal Removal Time Removal Pathology Group Dose Level Sex Animal Cage Day Week Date Time Slot Symptom Reason 7030 4 27/10/16 7:00 512 mg/kg/day Male 15 29 Term Term 2 30 28/10/16 512 mg/kg/day Female 7031 16 6:54 Term Term 7032 16 30 28/10/16 6:54 Term Term 7033 17 30 28/10/16 6:55 Term Term 7034 30 28/10/16 17 6:55 Term Term 7035 18 30 28/10/16 6:55 Term Term 7036 18 30 28/10/16 6:56 Term Term 7037 19 30 28/10/16 6:56 Term Term 7038 19 30 28/10/16 6:56 Term Term 7039 20 30 28/10/16 6:57 Term Term 7040 20 28/10/16 6:57 Term 30 Term 7041 27/10/16 7:00 Term Term 1024 mg/kg/day Male 21 29 7042 21 29 27/10/16 7:00 Term Term 27/10/16 7:01 7043 22 29 Term Term 7044 22 27/10/16 Term 29 7:01 Term 7045 23 29 27/10/16 7:02 Term Term 7046 23 29 27/10/16 7:02 Term Term 7047 24 29 27/10/16 7:03 Term Term 7048 24 29 27/10/16 7:03 Term Term 7049 25 29 27/10/16 7:04 Term Term 25 7050 29 27/10/16 7:04 Term Term 3 1024 mg/kg/day Female 7051 26 30 28/10/16 6:58 Term Term 7052 26 30 28/10/16 6:58 Term Term 7053 27 30 28/10/16 6:58 Term Term 7054 27 30 28/10/16 6:59 Term Term 7055 28 30 28/10/16 6:59 Term Term 28 Term 7056 30 28/10/16 6:59 Term 7057 29 30 28/10/16 6:59 Term Term

Individual Animal Fates

PSL Study Number 43166 A 28-Day Dietary Study in Rats

						oval	Removal	Removal	Time	Removal	Pathology
roup	Dose Level	Sex	Animal	Cage	Day	Week	Date	Time	Slot	Symptom	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 OBSERVATIONS1

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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.

Animal:	7001	Group:	1	Sex:	Male
Necropsy D	ate: 10/27/2016	Dose	0		
Crass Box	hology Observations [Correlation]:				
	noiogy observations (correlation):				
·					
	ning protocol required tissues, which have bee	s examined	have no visible lesions		
Animat:	7002	Group:	1	Sex:	Male
Necropsy D	ate: 10/27/2016	Dose	0		
	hology Observations [Correlation]:		······································		
	ibined : size: 1 x 1.5 cm				
	bined : right, small; soft				
	es-combined : size: 3 x 0.5 cm				
epididymid	es-combined : right, small				
Any remair	ning protocol required tissues, which have bee	n examined	have no visible lesions		
Animal:	7003	Group:	1	Sex:	Male
	ale: 10/27/2016	Dose:	0		
Gross Pat	hology Observations [Correlation]:				
Gross Pat No observi Any remain	ations found ning prolocol required tissues, which have bee				11.1
Gross Pat	ations found	Group:	1	Sex:	Male
Gross Pat No observa Any remsii Animal:	ations found ning prolocol required tissues, which have bee			Sex:	Male
Gross Pat No observe Any remain Animal: Necropsy D	ations found ing protocol required tissues, which have bee 7004 ate: 10/27/2016	Group:	1	Sex:	Male
Gross Pat No observi Any remain Animal: Necropsy D Gross Pat	stions found ing protocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations (Correlation):	Group:	1	Sex:	Male
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa	ations found ing protocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations (Correlation): ations found	Group: Dose:	1 0	Sex:	Male
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa	stions found ing protocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations (Correlation):	Group: Dose:	1 0		Male
Gross Pat No observe Any remain Animal: Necropsy D Gross Pat No observe Any remain	stions found ting prolocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: stions found hing prolocol required tissues, which have bee	Group: Dose: n examined	1 0 have no visible lesions		
Gross Pat No observa Anny remain Animal: Necropsy D Gross Pat No observa Any remain	stions found ting prolocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: stions found hing prolocol required tissues, which have bee	Group: Dose: n examined Group:	1 0 have no visible lesions		
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa Any remain	ations found aing protocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: ations found aing protocol required tissues, which have bee 7005	Group: Dose: n examined Group:	1 0 have no visible lesions		
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa Any remain Animal: Necropsy D Gross Pat	stions found ing prolocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: stions found hing prolocol required tissues, which have bee 7005 ate: 10/27/2016	Group: Dose: n examined Group:	1 0 have no visible lesions		
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa No observa	stions found ing prolocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: stions found have bee 7005 ate: 10/27/2016 hology Observations [Correlation]:	Group: Dose: n examined: Group: Dose:	1 0 have no visible lesions 1 0		
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa Any remain Animal: Necropsy D Gross Pat No observa No observa	stions found ing prolocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: stions found ing prolocol required tissues, which have bee 7005 ate: 10/27/2016 hology Observations [Correlation]: stions found	Group: Dose: n examined: Group: Dose:	1 0 have no visible lesions 1 0	Sex:	
Gross Pat No observa Any remain Animal: Necropsy D Gross Pat Any remain Animal: Necropsy D Gross Pat Any remain Animal: Necropsy D Any remain Any remain	ations found ing prolocol required tissues, which have bee 7004 ate: 10/27/2016 hology Observations [Correlation]: stions found hing prolocol required tissues, which have bee 7005 ate: 10/27/2016 hology Observations [Correlation]: stions found	Group: Dose n examined Group: Dose:	1 0 have no visible tesions 1 0 have no visible lesions	Sex:	Male

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:	Maic
Necropsy Date: 10/27/2016	Dose:	0		
nectopsy date. 10/2/1/2010				
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
Necropsy Date: 10/27/2016	Dose	0		
Gross Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which have				
Animal: 7010	Group: Dose:	1	Sex:	Mate
Necropsy Date: 10/27/2016	Dose.	U		
	•			
Gross Pathology Observations (Correlation): No observations found				
Any remaining protocol required tissues, which have				
Animal: 7011	Group: Dose:	1	Sex	Female
Necropsy Date: 10/28/2016	5002	•		
Corne Bathelese Observations (Name 1-1)				
Gross Pathology Observations [Correlation]: No observations found				
		have no visible lesions		
Any remaining protocol required tissues, which have Animal: 7012		nave no visible resions	e	Female
numa. 1912	Group: Dose:	0	Sex:	remaje
Necropsy Date: 10/28/2016				

No observations found	•			
Any remaining protocol req	uired tissues, which have been examined,	have no visible lesions		
Animal: 7013	Group:	1	Sex: Fe	emale
No.	Dose	0		
Necropsy Date: 10/28/2016	3			
Gross Pathology Observa	ations [Correlation]:			
uterus ; fluid filled				
Any remaining protocol req	uired tissues, which have been examined,	have no visible tesions		
Animal: 7014	Group:	1	Sex: Fe	male
	Dose	0		
Necropsy Date: 10/28/2016	<u> </u>			
Gross Pathology Observa	ations [Correlation]:			
No observations found	-			
Any remaining protocol rec	uired tissues, which have been examined,	have no visible lesions		
Animal: 7015	Group:	1	Sex: Fe	emale
	Dose	0		
Necropsy Date: 10/28/2016	6			
Gross Pathology Observ	ctions [Correlation]:			
No observations found	aiona (obtientatori).			
	uivad liannaa uubiah hava haan araasinad	have as visible tosions		
	ured lissues, which have been examined		Sex: Fe	
Animal: 7016	Group: Dose:	1 0	Şex; re	CLUSHAC
Necropsy Date: 10/28/2016		•		
Gross Pathology Observ	ations [Correlation]:			
No observations found				
Any remaining protocol req	uired tissues, which have been examined	have no visible lesions		
Animal: 7017	Group:	1	Sex: Fe	emele
Necropsy Date: 10/28/2010	Dos∉ s	0		
Necropsy Date: 10/28/2019	U			
	ations [Correlation]:			
Gross Pathology Observ	• •			
Gross Pathology Observuterus: fluid filled	• •			
uterus : fluid filled	quired bissues, which have been examined	have no visible lesions		
uterus : fluid filled		have no visible lesions	Sex: Fe	emale

Gross Pathology Observations (Correlation	n]:			
uterus : fluid filled				
Any remaining protocol required tissues, which	h have been examined	have no visible lesions		
Animal: 7019	Group:	1	Sex:	Female
	Dose:	0		
Necropsy Date: 10/28/2016				
Gross Pathology Observations [Correlation	n]:			
No observations found				
Any remaining protocol required tissues, which	h have been examined	have no visible lesions		
Animal: 7020	Group:	1	Sex:	Female
	Dose	0		
Necropsy Date: 10/28/2016				
Gross Pathology Observations [Correlation	n]:			
uterus : fluid filled	•			
Any remaining protocol required tissues, which	h have been examined	, have no visible lesions		
Animal: 7021	Group:	2	Sex:	Male
	Dose	512		
Necropsy Date: 10/27/2016				
Gross Pathology Observations (Correlation	n]:			
No observations found	-			
Any remaining protocol required tissues, which	h have been examined	have no visible lesions		
Animal: 7022	Group:	2	Sex:	Male
	Dose	512		
Necropsy Date: 10/27/2016	٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠			
Gross Pathology Observations (Correlation	n):			
No observations found	•			
Any remaining protocol required tissues, which	h have been examined	have no visible lesions		
Animal: 7023	Group:	2	Sex:	Male
	Dose:	512	 -	
Necropsy Date: 10/27/2016				
Gross Pathology Observations (Correlation	nl:			
No observations found	•			
Any remaining protocol required basues, which	h have been examined	have no visible lesions		
Animal: 7024	Group;	2	Sex	Male
	-, ουρ.	-	JUA.	

	Dose	512	
lecropsy Date: 10/27/2016			
Gross Pathology Observations [Correlation]:			
No observations found			
Any remaining prolocol required tissues, which have t	neen examined	have no visible lesions	
knimal: 7025	Group:	2	Sex: Male
lecropsy Dale: 10/27/2016	Dose	512	
Gross Pathology Observations [Correlation]:			
No observations found			
Any remaining prolocol required tissues, which have t	been examined	have no visible lesions	
nimal: 7026	Group:	2	Sex: Mate
lecropsy Date: 10/27/2016	Dose	512	
Gross Pathology Observations (Correlation):			
No observations found			
Any remaining protocol required tissues, which have t	seen examined	have no visible lesions	
unimal: 7027	Group:	2	Sex: Male
	Dosec	512	
lecropsy Dale: 10/27/2016			
Gross Pathology Observations [Correlation]:			
Gross Pathology Observations [Correlation]: No observations found	oeen examined	have no visible lesions	
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have t	oeen examined. Group:	have no visible lesions	Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to nimal: 7028			Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to	Group:	2	Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to immal: 7028 Jacopsy Date: 10/27/2016	Group:	2	Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to immel: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]:	Group:	2	Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have I unimal: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]: No observations found	Group: Dose:	2 512	Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to unimal: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to	Group: Dose:	2 512	Sex: Male Sex: Male
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to unimal: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]; No observations found Any remaining protocol required tissues, which have to unimal: 7029	Group: Dose: Dose:	2 512 have no visible lesions	
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to unimal: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to	Group: Dose: Dose: Dose: Oseen examined. Group:	2 512 have no visible lesions 2	
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to nimal: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to nimal: 7029 lecropsy Date: 10/27/2016	Group: Dose: Dose: Dose: Oseen examined. Group:	2 512 have no visible lesions 2	
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to unimal: 7028 lecropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]; No observations found Any remaining protocol required tissues, which have to unimal: 7029	Group: Dose: Dose: Dose: Oseen examined. Group:	2 512 have no visible lesions 2	

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Animal: 7030	Group:	2	Sex:	Male
J	Dose:	512		
Vecropsy Date: 10/27/2016				
Gross Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which ha	ave 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 ha	eve been examined	have no visible lesions		
Animal: 7032	Group:	2	Sex	Female
	Dose:	512		
Necropsy Date: 10/28/2016				
Any remaining protocol required tissues, which ha Animal: 7033	Group:	have no visible lesions 2 512	Sex:	Female
Necropsy Date: 10/28/2016	Dusc.	512		
0 0-th-1 05				
Gross Pathology Observations [Correlation]:				
No shannations found				
No observations found		Same and Addition to the		
Any remaining protocol required tissues, which ha				
Any remaining protocol required tissues, which ha	Group:	have no visible lesions 2 512	Sex:	Female
Any remaining protocol required tissues, which ha Animal: 7034		2	Sex:	Female
Any remaining protocol required tissues, which he Animal: 7034 Necropsy Date: 10/28/2016	Group:	2	Sex:	Female
Any remaining protocol required tissues, which he Animal: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]:	Group:	2	Sex	Female
Any remaining protocol required tissues, which he Anima: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found	Group: Dose:	2 512	Sex:	Female
Any remaining protocol required tissues, which he Anima: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which he	Group: Dose: we been examined,	2 512 have no visible lesions		
Any remaining protocol required tissues, which he Animal: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which he	Group: Dose: Ne been examined, Group:	2 512 have no visible lesions 2		Female
Any remaining protocol required tissues, which he Animal: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which he Animal: 7035	Group: Dose: we been examined,	2 512 have no visible lesions		
Any remaining protocol required tissues, which he Animal: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which he Animal: 7035	Group: Dose: Ne been examined, Group:	2 512 have no visible lesions 2		
Any remaining protocol required tissues, which he Animal: 7034 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which he Animal: 7035	Group: Dose: Ne been examined, Group:	2 512 have no visible lesions 2		

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y . in any . no con desce knowly (reches		b, Moderate (C) Alopecia, Righ	f Forelimb, Moderate (CII)	
Any remaining protocol required tissues, which have t				
nimal; 7036	Group:	2	Cau-	Female
omina, 1909	Dose.	512	364.	, Giller
Necropsy Date: 10/28/2016	2002			
Gross Pathology Observations [Correlation]:				
No observations found				
·		have as visible facions		
Any remaining protocol required tissues, which have t Animal: 7037		1 nave no visible lesions		Female
equinitie. 7037	Group: Dose:	512	36%.	remane
Necropsy Date: 10/28/2016	2000.			
Gross Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which have t	een examined	have no visible lesions		
Animal: 7038	Group:	2	Sex:	Female
	Dose:	512		
Necropsy Date: 10/28/2016			_	
non-national at the fact to				
Gross Pathology Observations [Correlation]:				
Gross Pathology Observations [Correlation]: No observations found				
•	oeen exemined	have no visible lesions		
No observations found Any remaining protocol required tissues, which have to	oeen examined Group;	2	Sex	Female
No observations found Any remaining protocol required tissues, which have technical: 7039			Sex	Female
No observations found Any remaining protocol required tissues, which have technical: 7039	Group:	2	Sex	Female
No observations found Any remaining protocol required tissues, which have technical: 7039	Group:	2	Sex:	Female
No observations found Any remaining protocol required tissues, which have telephone from the following the followi	Group:	2	Sex:	Female
No observations found Any remaining protocol required tissues, which have tended to the second seco	Group: Dose:	2 512	Sex	Female
No observations found Any remaining protocol required tissues, which have tendered tissues, which have	Group: Dose: Dose:	2 512		Female
No observations found Any remaining protocol required tissues, which have tendered tissues, the tissue tendered tissues, the tissue tendered tissues, the tissues, the tissue tendered tissues, the tissue tendered tissues, the tissue tendered tissues, the tissue tendered tissues, the tissues, the tissue tendered tissues, the tissues, the tissue tendered tissues, the tissue tendered tissues, the tissue tendered tissues, the tissues, the tissue tendered tissues, the tissue tende	Group: Dose:	2 512 have no visible lesions		
No observations found Any remaining protocol required tissues, which have tendered tissues, which have	Group: Dose: Dose: Dose: Oseen examined Group:	2 512 have no visible lesions		
No observations found Any remaining protocol required tissues, which have to Animal: 7039 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to Animal: 7040 Necropsy Date: 10/28/2016	Group: Dose: Dose: Dose: Oseen examined Group:	2 512 have no visible lesions		
No observations found Any remaining protocol required tissues, which have tender of the company	Group: Dose: Dose: Dose: Oseen examined Group:	2 512 have no visible lesions		
No observations found Any remaining protocol required tissues, which have to Animal: 7039 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to Animal: 7040 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]:	Group: Dose: Dose: Dose: Dose:	2 512 have no visible lesions 2 512		
No observations found Any remaining protocol required tissues, which have the Animal: 7039 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have the Animal: 7040 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have the Animal to the Anim	Group; Dose: Dose: Dose: Dose:	2 512 have no visible lesions 2 512	Sex:	
No observations found Any remaining protocol required tissues, which have to Animal: 7039 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to Animal: 7040 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have to observations found Any remaining protocol required tissues, which have the content of the content o	Group: Dose: Dose: Dose: Dose:	2 512 have no visible lesions 2 512	Sex:	Female

No observations found				
Any remaining protocol required tissues, which I	have been examined	have no visible lesions		
Animal: 7042	Group:	3	Sex:	Male
	Dose	1024		
Necropsy Date: 10/27/2016				
Groza Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which I	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 I	nave been examined	have no visible lesions		
Animal: 7044	Group;	3	Sex:	Male
	Dose	1024		
Necropsy Date: 10/2772016 Gross Pathology Observations [Correlation]: No observations found				
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which i		have no visible lesions	Sex	Male
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which i Animal: 7045	nave been examined		Sex	Male
No observations found Any remaining protocol required tissues, which t	nave been examined. Group:	3	Sex	Male
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which i	nave been examined, Group: Dose:	3	Sex	Male
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7045 Necropsy Date: 10/27/2016	nave been examined, Group: Dose:	3	Sex	Male
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation):	nave been examined Group: Dose:	3 1024	Sex	Male
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which i Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found	nave been examined Group: Dose:	3 1024 have no visible lesions 3		Male
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which i Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which i Animal: 7046	nave been examined, Group: Dose:	3 1024 have no visible lesions		
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which is Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which is Animal: 7046	nave been examined. Group: Dose: nave been examined. Group:	3 1024 have no visible lesions 3		
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which is Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which is Animal: 7046	nave been examined, Group: Dose: nave been examined, Group: Dose:	3 1024 have no visible lesions 3		
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7046 Necropsy Date: 10/27/2016	nave been examined, Group: Dose: nave been examined, Group: Dose:	3 1024 have no visible lesions 3		
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7046 Necropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]:	nave been examined. Group: Dose: nave been examined. Group: Dose:	3 1024 have no visible lesions 3 1024		
Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7045 Necropsy Date: 10/27/2016 Gross Pathology Observations (Correlation): No observations found Any remaining protocol required tissues, which it Animal: 7046 Necropsy Date: 10/27/2016 Gross Pathology Observations [Correlation]: No observations found	nave been examined. Group: Dose: nave been examined. Group: Dose:	3 1024 have no visible lesions 3 1024	Sex:	

Any remaining protocol remared liceuses	, which have been examined, have no visible lesions	
Animai: 7048	Group; 3	Sex: Male
rvinista, 10-70	Dose 1024	OUN, IMPO
Necropsy Date: 10/27/2016		
Gross Pathology Observations (Corn	efation):	
No observations found		
	; which have been examined, have no visible lesions	
Animal: 7049	Group: 3	Sex: Male
	Dose: 1024	
Necropsy Date: 10/27/2016		
Gross Pathology Observations [Com	elation]:	
No observations found		
	s, which have been examined, have no visible lesions	
Animal: 7050	Group: 3	Sex: Male
	Dose: 1024	
Necropsy Date: 10/27/2016		
Gross Pathology Observations [Corr	nlation!	
No observations found	sionenj.	
	s, which have been examined, have no visible lesions	
Animal: 7051	Group: 3 Dose: 1024	Sex: Female
Necropsy Date: 10/28/2016	Dose: 1024	
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
Gross Pathology Observations (Corr	elation]:	
No observations found		
Any remaining protocol required tissues	, which have been examined, have no visible lesions	
	Group: 3	Sex; Female
Animal: 7052	Dose: 1024	
	DUSC 1024	
	1056 1024	
Necropsy Date: 10/28/2016		
Necropsy Date: 10/28/2016 Gross Pathology Observations (Corr No observations found	elation]:	
Necropsy Date: 10/28/2016 Gross Pathology Observations (Corr No observations found		Sex: Female

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 bissues, 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 I	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				
	haan mamirad	have no visible legione		
Any remaining prolocol required tissues, which have I Animal: 7059		nave no visible lesions	A	Female
Animai: 7059	Group:	3	Sex:	remale

Necropsy Date: 10/28/2016	Dose:	1024		
Gross Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which have t	oeen examined	have no visible lesions		
Animai: 7060	Group:	3	Sex:	Female
Necropsy Date: 10/28/2016	Dose	1024		
Gross Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which have t	neen 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 t	seen 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 t	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 t	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				
		have no visible lesions		

Animal:	7065	Group: 4 Dose: 1536	Sex: Male
Necropsy Date	e: 10/27/2016	Dose 1330	
Gross Patho	ology Observations (Correlation	nl'	
No observation		·· ·	
		th have been examined, have no visible lesions	
	7066	Group: 4	Sex: Male
, _,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	, 444	Dose: 1536	
Necropsy Date	10/27/2016		
Gross Patho	logy Observations (Correlatio	n]:	
No observation	**		
Any remainin	g protocol required tissues, whic	th have been examined, have no visible lesions	
······································	7067	Group: 4	Sex: Male
		Dose: 1536	
Necropsy Date	: 10/27/2016		
Animal:	7068	Group: 4 Dose: 1536	Sex: Male
Necropsy Date	e: 10/27/2016	Dose 1300	
Grone Patho	logy Observations [Correlatio	n]·	
No observation	-	иј.	
		har in the state of the state of	
	g protocol required assures, while	h have been examined, have no visible lesions Group: 4	Sex: Male
Autina.	1009	Group: 4 Dose: 1536	Зех. Іиме
Necropsy Date	: 10/27/2016		
Last Clinical	Observations:		
Eschar, Head	L Superficial		
Gross Patho	logy Observations (Correlatio	n]:	
	d finding : no correlated finding	[Eschar, Head, Superficial (C)]	
non correlate		h have have accepted however of the last on	
	g protocol required tissues, whic	n nave been examined, have no visible lesions	
Any remainin	g protocol required tissues, which 7070	Group: 4	Sex: Male
Any remainin	7070		Sex: Made

Gross Pathology Observations [Correlation]:				
No observations found				
Any remaining protocol required tissues, which have t	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				
		have an visible lecione		
Any remaining protocol required tissues, which have Animal: 7073		4	Car	Female
Malamia, 1073	Group: Dose:	1536	Sex.	rçıllalç
Necropsy Date: 10/28/2016	2000	1000		
Gross Pathology Observations [Correlation]:				•
	been examined, Group: Dose:	have no visible lesions 4 1536	Sex:	Female
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have	Group:	4	Sex	Female
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074	Group: Dase:	4 1536	Sex:	Female
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found	Group: Dase:	4 1536		Female
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have	Group: Dose: been examined.	4 1536 have no visible lesions		
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have	Group: Dose: been examined: Group:	4 1536 have no visible lesions		
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7075 Necropsy Date: 10/28/2016	Group: Dose: been examined: Group:	4 1536 have no visible lesions		
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7075 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]:	Group: Dose: been examined: Group:	4 1536 have no visible lesions		
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7075 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found	Group: Dose: been examined: Group: Dose.	4 1536 have no visible lesions 4 1536		
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7075 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: Oross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have	Group: Dose: been examined: Group: Dose.	4 1536 have no visible lesions 4 1536 have no visible lesions	Sex:	Female
Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7074 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found Any remaining protocol required tissues, which have Animal: 7075 Necropsy Date: 10/28/2016 Gross Pathology Observations [Correlation]: No observations found	Group: Dose: been examined: Group: Dose.	4 1536 have no visible lesions 4 1536	Sex:	

No observations found				
Any remaining protocol required bissues, with	ich have been examined, hav	e no visible lesions		
Animal: 7077	Group: 4		Sex:	Female
	Dose: 1	536		
Necropsy Date: 10/28/2016				
Gross Pathology Observations [Correlati	on]:			
No observations found				
Any remaining protocol required tissues, wh	ich have been examined, hav	re no visible lesions		
Animal: 7078	Group; 4		Sex:	Female
	Dose: 1:	536		
Necropsy Date: 10/28/2016				
Any remaining prolocal required lissues, who	ich have been examined hav	e no visible lesions		
Any remaining prolocol required bissues, wh Animal: 7079			Sex:	Female
	Group: 4		Sex:	Female
Animal: 7079	Group: 4	<u> </u>	Sex:	Female
Animal: 7079	Group: 4 Dose 1:	<u> </u>	Sex:	Female
Animal: 7079 Necropsy Date: 10/28/2016	Group: 4 Dose 1:	<u> </u>	Sex:	Female
Animal: 7079 Necropsy Date: 10/28/2016 Gross Pathology Observations (Correlati	Graup: 4 Dose: 1: on]:	536	Sex:	Female
Animal: 7079 Necropsy Date: 10/28/2016 Gross Pathology Observations (Correlati No observations found Any remaining protocol required tissues, wh	Group: 4 Dose: 1: on]: ich have been examined, hav Group: 4	e no visible lesions		Female
Animal: 7079 Necropsy Date: 10/28/2016 Gross Pathology Observations (Correlati No observations found Any remaining protocol required tissues, wh Animal: 7080	Group: 4 Dose: 1: on]: ich have been examined, hav Group: 4	536		
Animal: 7079 Necropsy Date: 10/28/2016 Gross Pathology Observations (Correlati No observations found Any remaining protocol required tissues, wh Animal: 7080	Group: 4 Dose: 1: on]: ich have been examined, hav Group: 4	e no visible lesions		
Animal: 7079 Necropsy Date: 10/28/2016 Gross Pathology Observations (Correlati No observations found Any remaining protocol required tissues, wh Animal: 7080	Group: 4 Dose: 1: on]: ich have been examined, hav Group: 4 Dose: 1:	e no visible lesions		
Animal: 7079 Necropsy Date: 10/28/2016 Gross Pathology Observations (Correlati No observations found Any remaining protocol required tissues, wh Animal: 7080 Necropsy Date: 10/28/2016	Group: 4 Dose: 1: on]: ich have been examined, hav Group: 4 Dose: 1:	e no visible lesions		
Animal: 7079 Recropsy Date: 10/28/2016 Gross Pathology Observations (Correlating No observations found Any remaining protocol required tissues, which will be a recropsy Date: 10/28/2016 Gross Pathology Observations (Correlating Correlating Cor	Group: 4 Dose: 1: ich have been examined, hav Group: 4 Dose: 1:	e no visible lesions		

APPENDIX Q: INDIVIDUAL ANIMAL TERMINAL BODY AND ORGAN WEIGHTS¹

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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.

o 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)
ļ		-				-	b+
7001	399	0.073	2.19	1.14	1.31	3.19	11.08
7002	359	0.071	2.16	0.94	1.13	281	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

0 mg/kg/day Group 1	Spicen Wt (g)	Testes Wt (g)	Thymus Wi (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	243	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

ex: Male Day(s)	,			-			
ng/kg/day Group 2	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Epididymides Wt (g)	Heart Wt (9)	Kidneys Wt (9)	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

512 mg/kg/day Group 2	Spicen 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	295	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

1024 ng/kg/day Group 3	Terminal BW (9)	Adrenal Glands Wt (g)	Brain Wt (g)	Epididymides Wt (g)	Heart Wt (9)	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	291	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	

1024 mg/kg/day Group 3	Spicen Wt (g)	Wt Wt	
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

t536 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)
<u> </u>	ы.						
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

1536 mg/kg/day	Spleen	Testes	Thymus	
Group 4	(9) Wt	(g)	Wt (9)	
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	

0 mg/kg/day Group 1	BW Gland	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wi (g)	Kidneys Wt (g)	Liver Wt (g)	Ovaries with Oviducts Wt (g)
	-	-	<u>-</u>	-	-	-	•
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

o mg/kg/day Group 1	Spicen Wt (9)	Thymus Wt (g)	Uterus Wt (g)
	<u>-</u>	•	
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

i12 ng/kg/day Group 2	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wit (9)	Kidneys Wt (9)	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

512	(s) Relative to Start Date		
mg/kg/day Group 2	Spicen 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

024 ng/kg/day Broup 3	Terminal BW (9)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Ovaries with Oviducts Wt (g)
<u> </u>	·	-		•		-	-
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

1024				
mg/kg/day Group 3	Spieen	Thymus	Uterus Wt	
Situato 2	Wt	Wt (
	(9)	(g)	(g)	
	-	<u>-</u>		
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	

1536 mg/kg/day Terminal Group 4 BW (g)	BW	Adrenal Glands Wt (g)	Brain Wt (9)	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
иl	10	10	10	10	10	10	10

1536 mg/kg/day Group 4	Spicen Wt (g)	Thymus Wt (g)	Literus Wt (9)
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 RATIOS1

PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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.

0 mg/kg/day Group 1	Adrenal /TBW (Ratio)	Brain /TBW (Ralio)	Epiddymides /TBW (Ratio)	Heart //BW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spicen /TBW (Ratio)
	-	<u>-</u>	· · · · · · · · · · · · · · · · · · ·	•	•	•	•
7001	0.183	5.49	2.857	3.28	7.99	27.77	2.16
7002	0.198	6.02	2618	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	2514	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

0		
mg/kg/day Group 1	Testes /TBW (Ratio)	Thymus /TBW (Ralio)
	•	
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

512 ng/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

512 mg/kg/day Group 2	Testes /TBW (Ratio)	Thymus ITBW (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	

1024 mg/kg/day Group 3	Adrenal /TBW (Ratio)	Brain /ТВW (Ratio)	Epididymides /TBW (Ratio)	Heart /ТВW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spicen /TBW (Ratio)
	<u>-</u>	<u> </u>	-	-	-	-	-
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

1024			
mg/kg/day Group 3	Testes /TBW (Ratio)	Thymus /TBW (Ratio)	
	-	<u>-</u>	
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	

1536 ng/kg/day Group 4	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Epididymides /TBW (Ratio)	Heart /ТВW (Ratio)	Kidneys ЛВW (Ratio)	Liver /TBW (Ratio)	Spicen /TBW (Ratio)
	•	•	<u> </u>	•	•	•	•
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

Sex Male Day(s)	Relative to Start Date	
mg/kg/day Greup 4	Testes /ТВW (Ratio)	Thymus /TBW (Ralio)
	•	-
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	0.865	0.2919
N	10	10

0 mg/kg/day Group 1	Adrenal /ТВW (Ratio)	Brain /ТВW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver ЛВW (Ratio)	Overies with oviduots/TBW (Ratio)	Spieen /TBW (Ratio)
		-	•	<u>.</u>	<u>-</u>	-	•
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

	(s) Relative to Start Date	
0 nig/kg/day Group 1	Thymus /TBW (Ratio)	Uterus /TBW (Ratio)
	-	•
7011	1.902	2.94
7012	1.252	291
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 N	10	10

512 ng/kg/day Group 2	Adrenal /ТВW (Ratio)	Brain /TBW (Ratio)	Heart ЛВW (Ratio)	Kidneys //BW (Ratio)	Liver /T8W (Ratio)	Ovaries with oviduets/TBW (Ratio)	Spicen /TBW (Ratio)
	•	•	<u> </u>	•		•	-
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

	(s) Relative to Start Date		
512 mg/kg/day			
Group 2	Thymus /TBW (Ratio)	Uterus /TBW (Ralio)	
_		•	
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	
иl	10	10	

1024 mg/kg/day Group 3	Adrenal /TBW (Ratio)	Brain /TBW (Ralio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Overies with oviducts/TBW (Ratio)	Spicen /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

Sex Female Day	(s) Relative to Start Date	
1024		
mg/kg/day Group 3	Thymus ЛВW (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

1536 ng/kg/day Group 4	Adrenal /TBW (Ralio)	8rain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /T8W (Ratio)	Overies with oviduots/TBW (Ratio)	Spleen /TBW (Ratio)
(1000)	(Maile)	(runo)	(riducy	((Care)	frames)	(resto)	
	-	•	•		•	-	•
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

Sex Female	Day(s) Relative to Start Dat	e
1536 mg/kg/day Group 4	Thymus /TBW (Ratio)	Uteris ITBW (Ratio)
	-	-
7071	2,736	1.96
7072	1.978	2.24
7073	1.553	213
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

[[]organ weight/brain weight]

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.

) ng/kg/day Group 1	Adrenal /BrW (Ratio)	Epididymides /BrW (Relio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Testes /BrW (Rabo)	
		-	-	-			-	
7001	0.033	0.521	0.60	1.45	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	0.496	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	

512 mg/kg/day Group 2	Adrenal /BrW (Ratio)	Epididymides /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ralio)	Tesles /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	1.591
SD	0.0056	0.0535	0.048	0.100	0.374	0.055	0.155
N	10	10	10	10	10	10	10

iex Male Day(s)	Relative to Start Date	
512		
mg/kg/day	Thymus	
Group 2	/BrW	
	(Ratio)	
	<u> </u>	
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	

1024 ng/kg/day Group 3	Adrenal /BrW (Ratio)	Epididymides /BrW (Ralio)	Heart ÆrW (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	1.57	
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	0.652	0.114	0.740	0.039	0.123	
N	10	10	10	10	10	10	10	

Sex Male Da	y(s) Relative to Start Date
1024 mg/kg/day Group 3	Thymus /B/W (Ratio)
70.14	
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

1536 ng/kg/day Group 4	Adrenal /BrW (Ratio)	Epididymides /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Testes /BrW (Retio)
-		-		-	-	-	•
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
\$D	0.0039	0.0573	0.027	0.078	0.579	0.044	0.125
N	10	10	10	10	10	10	10

Sex: Male Da	y(s) Relative to Start Date
1536 mg/kg/day Group 4	Thymus iBrW (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

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

520

Individual Animat 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 (Rafio)
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
Wean	0,361
S	0.118

Sex Female	Day(s) Relative to Start Date
0	
mg/kg/day Group 1	Utenus ABrW
••••	(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
S	0.118

512							
ng/kg/day Group 2	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Ovaries with oviduds/BrW (Rabo)	Spleen /BrW (Ratio)	Thymus /BrW (Retio)
	-	-	•	•	-	-	-
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
SĐ	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 Weigh Ratios

PSL Study Number 43166 A 28-Day Dietary Study in Rats

•																	
Day(s) Kelative to Start Date		Clens	(Ratio)	•	0.23	0.26	0.27	0.21	0.20	0.23	0.29	0.24	0.19	0.20	0.232	0.033	-
Sex Female	512	mg/kg/day Group 2			7031	7032	7033	7034	7035	7036	7037	7038	7039	7040	Nean	SD	Z
-																	

1024 mg/kg/day Group 3	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /B:W (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
	(Ratio)
	,
7051	0.21
7052	0.22
7053	0.62
7054	0.27
7055	0.31
2056	0.21
7057	0.25
7058	0.21
7059	0.46
7060	0.25
Mean	0.301
S	0.136
-	ç

1536 11g/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

		URerus (Baylo) (Redio) 0.23 0.26 0.27 0.24 0.24 0.19 0.21 0.27	1536 Group 4 Group 4 7071 7073 7073 7075 7075 7075 7075 7077 7075 7075
Mean 0.242		0.242	Wean
		_	_
		0,21	8707
		0.21	8/0/
		0.19	7077
		0.24	7076
		0.24	7075
		0.25	7074
		0.27	7073
		0.26	7072
····		0.23	1/0/
		,	
•	,		
		(Ratio)	
) 1986 ·).	Utens ABrW	mg/kg/day Group 4
(Redi (Redi 777 777 777 778 788 789	(Redin 1777 7777 7777 7777 7777 777 777 777 7		9891