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201-16358B

TEST SUBSTANCE

- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)
Source: Cardolite Corporation, Lot No.: AZ-0192

METHOD

- **Method/guideline followed:** OECD TG 422
- **Test type:** Oral gavage combined repeat dose toxicity study with reproduction/developmental toxicity screening
- **GLP:** Yes
- **Year:** 2005
- **Species:** Rat
- **Strain:** Sprague-Dawley Crl:CD® (SD) IGS BR
- **Route of administration:** oral (gavage)
- **Duration of test:** Up to 49 days
- **Doses/concentration levels:** 0, 15, 150 or 1000 mg/kg bw/day
- **Sex:** male/female
- **Exposure period:** Up to 49 days
- **Frequency of treatment:** Daily
- **Control group and treatment:** Yes. Arachis oil, 4 mL/kg bw/day
- **Post exposure observation period:** none
- **Premating exposure period for males:** 14 days
- **Premating exposure period for females:** 14 days

Statistical methods:

Data were processed to give group mean values and standard deviations where appropriate.

Haematological, blood chemical, organ weight (absolute and relative to terminal bodyweight), weekly bodyweight gain, litter weights, offspring bodyweights and quantitative functional

performance data were assessed for dose response relationships by linear regression analysis, followed by one way analysis of variance (ANOVA) incorporating Levene's test for homogeneity of variance. Where variances were shown to be homogenous, pairwise comparisons were conducted using Dunnett's test. Where Levene's test showed unequal variances the data were analysed using non-parametric methods: Kruskal-Wallis ANOVA and Mann-Whitney 'U' test.

The non-parametric methods were also used to analyse implantation loss, offspring sex ratio and landmark developmental markers.

The haematology variable basophils was not analysed since consistently greater than 30% of the data were recorded as the same value.

Remarks:

- **Test animals**
  - **Parental:** 10 males/10 females per dose
- **Test design**
  - **Vehicle:** Arachis oil BP
  - **Dosing schedules and pre and post dosing observations periods:**

    Parental: Animals dosed for 14 days prior to mating up to a total of 49 days.
- **Mating procedures:** Animals were paired on a 1 male: 1 female basis within each dose group, for a period of up to fourteen days. Cage tray-liners were checked each morning for the presence of ejected copulation plugs and each female was examined for the presence of a copulation plug in the vagina. A vaginal smear was prepared for each female and the stage of the oestrous cycle or the presence of sperm was recorded. The presence of sperm within the vaginal smear and/or vaginal plug *in situ* was taken as positive evidence of mating and the males were subsequently returned to their original holding cages. Mated females were housed individually during the period of gestation and lactation.

- **Standardization of litters:** No
- **Parameters assessed during study P and F1 as appropriate:**
  - **Clinical observations performed and frequency:**

    Clinical Observations: All animals were examined for overt signs of toxicity, ill-health and behavioural change immediately before and after dosing, and one and five hours after dosing, during the working week. Animals were observed immediately before and after dosing, and one hour after dosing at weekends.

    Bodyweight: Individual bodyweights were recorded on Day 0 (the day before the start of treatment) and then weekly for males until termination. Females were weighed weekly until mating was evident. Bodyweights were then recorded on Day 0, 7, 14 and 21 post coitum, and on Day 1 and 4 post partum.

    Food Consumption: During the maturation period, weekly food consumption was recorded for each cage of adults. For females showing evidence of mating, food consumption was recorded for the periods covering Days 1 - 7, 7 - 14 and 14 - 20. For

females with live litters, food consumption was recorded for the period covering Days 1 to 4 post partum.

Water Consumption: Water intake was observed daily by visual inspection of water bottles for any overt change.

- **Functional observations performed and frequency:**

  Prior to the start of treatment and at weekly intervals for four weeks, all animals were observed for signs of functional/behavioural toxicity. Functional performance tests were also performed on five selected males and females per dose level, prior to termination, together with an assessment of sensory reactivity to difference stimuli.

- **Behavioural assessments performed and frequency:**

  Detailed individual clinical observations were performed for each animal using a purpose-built arena. The following parameters were observed: Gait; Tremors; Twitches; Convulsions; Bizarre/Abnormal/Stereotypic behaviour; Salivation; Pilo-erection; Exophthalmia; Lachrymation; Hyper/Hypothermia; Skin colour; Respiration; Palpebral closure; Urination; Defecation; Transfer arousal; Tail elevation.

- **Functional performance tests performed and frequency:**

  Motor Activity: Purpose-built 44 infra-red beam automated activity monitors were used to assess motor activity. Animals were randomly allocated to the activity monitors. The tests were performed at approximately the same time each day, under similar laboratory conditions. The evaluation period was one hour for each animal. The percentage of time each animal was active and mobile was recorded for the overall one hour period and also during the final 20% of the period (considered to be the asymptotic period).

  Forelimb/Hindlimb Grip Strength: An automated grip strength meter was used. Each animal was allowed to grip the proximal metal bar of the meter with its forepaws. The animal was pulled by the base of the tail until its grip was broken. The animal was drawn along the trough of the meter by the tail until its hind paws gripped the distal metal bar. The animal was pulled by the base of the tail until its grip was broken. A record of the force required to break the grip for each animal was made. Three consecutive trials were performed for each animal.

- **Sensory reactivity tests performed and frequency:**

  Each animal was individually assessed for sensory reactivity to auditory, visual and proprioceptive stimuli. The following parameters were observed: Grasp response; Vocalisation; Toe pinch; Tail pinch; Finger approach; Touch escape; Pupil reflex; Startle reflex; Blink reflex.

- **Laboratory investigations performed and frequency:**

  Hematological and blood chemical investigations were performed on five males and five females selected from each test and control group on Day 13 (day prior to pairing). Blood samples were obtained from the lateral tail vein. Blood samples were also taken prior to termination (Day 48) for five males per dose group, and during termination on

Day 5 *post* partum for all females but only values for five females were reported. Animals were not fasted prior to sampling.

Hematology: The following parameters were measured on blood collected into tubes containing potassium EDTA anti-coagulant: Hemoglobin (Hb); Erythrocyte count (RBC); Hematocrit (Hct); Erythrocyte indices (mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC)); Total leucocyte count (WBC); Differential leucocyte count (neutrophils (Neut), lymphocytes (Lymph), monocytes (Mono), eosinophils (Eos), basophils (Bas)); Platelet count (PLT). Prothrombin time (CT) and activated partial thromboplastin time (APTT) were assessed using samples collected into sodium citrate solution (0.11 mol/l).

Blood Chemistry: The following parameters were measured on plasma from blood collected into tubes containing lithium heparin anti-coagulant: Urea; Glucose; Total protein; Albumin; Albumin/Globulin (A/G) ratio (by calculation); sodium; potassium; chloride; calcium; Inorganic phosphorus; aspartate aminotransferase; alanine aminotransferase; alkaline phosphatase; creatinine; Total cholesterol; Total bilirubin.

- **Organs examined at necropsy (macroscopic and microscopic):**

Surviving adult females were killed by intravenous overdose of sodium pentobarbitone followed by exanguination on Day 5 post partum. Following the termination of all adult females, all surviving males were killed by intravenous overdose of sodium pentobarbitone followed by exsanguination.

All adult animals, including those dying during the study, were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

Organ Weights: The following organs, removed from adult animals that were killed at the end of the study, were dissected free from fat and weighed before fixation: Adrenals; brain, Epididymides; Heart; Kidneys; Histopathology; Liver; Ovaries; Spleen; Testes; Thymus.

Histopathology: Samples of the following tissues were preserved from five males and five females from each dose group, in buffered 10% formalin. The tissues shown in italics were also removed from the remaining animals: Adrenals; Aoarta (thoracic); Bone and bone marrow (sternum); Brain (including cerebrum, cerebellum and pons); Caecum; *Coagulating gland*; Colon; Duodenum; *Epididymides*; Eyes; Gross lesions; Heart; Ileum; Jejunum; Kidneys; Liver; Lungs (with bronchi); Lymph nodes (cervical and mesenteric);Mammary gland;Muscle (skeletal); *Ovaries*; Pancreas; *Pituitary; Prostate*; Oesophagus; Rectum; Salivary glands (submaxillary);Sciatic nerve; *Seminal vesicles*; Skin (hind limb); Spinal cord (cervical); Spleen; Stomach; Thyroid/parathyroid; Trachea; *Testes*; Thymus; Urinary bladder; *Uterus/cervix*; Vagina.

- **Estrous cycle length and pattern (number of days spent in each phase):** Not investigated
- **Sperm examination:** Not investigated

RESULTS

- **Parental NOEL:** 150 mg/kg bw/day

- **Offspring NOEL:** 1000 mg/kg bw/day
- **Actual dose received by dose level by sex:** 0, 15, 150 or 1000 mg/kg bw/day
- **Parental data and F1 as appropriate (toxic response/effects with NOAEL value). Provide at a minimum qualitative descriptions of elements where dose related observations were seen:** Refer to Remarks
- **Statistical results, as appropriate:** Refer to Remarks

Remarks:

- **Parental data:**
- **Body weight:** A slightly reduced bodyweight gain was observed for 1000 mg/kg/day males during the first two weeks of the study. Reduced bodyweight gain was also observed for 1000 mg/kg/day females during the later stages of the gestation period.
- **Food/water consumption:** No adverse effect on dietary intake or food efficiency was detected. No intergroup differences in water consumption were detected.
- **Description, severity, time of onset and duration of clinical signs:** Increased salivation was detected prior to dosing and up to five hours after dosing for animals of either sex treated with 1000 mg/kg/day from Day 9 onwards. An isolated incident of increased salivation was detected up to one hour after dosing for one male treated with 150 mg/kg/day on Day 8 only. One female treated with 150 mg/kg/day developed hunched posture, pilo-erection, tiptoe gait, red/brown staining around the mouth, laboured respiration and pallor of the extremities on Day 5 and was subsequently terminated due to the severity of these observations. On Day 39 of the study (gestation Day 21), one female treated with 1000 mg/kg/day showed staining around the vagina, hunched posture, tiptoe gait, pilo-erection, pallor of the extremities and red/brown staining around the snout. This animal had given birth to a total of sixteen pups, twelve of which were found dead. This animal, together with the live pups were subsequently terminated on humane grounds. No such observations were observed for animals of either sex treated with 15 mg/kg/day.
- **Fertility index:** No adverse effects were detected on mating performance or fertility. A reduced parturition index was evident at 1000 mg/kg/day, but this was attributed to the termination of one female due to dystocia (refer to Table 1 below)
- **Precoital interval (with number of days until mating and number of estrous periods until mating):** No treatment-related difference in precoital interval (refer to Table 1 below).
- **Duration of gestation (calculated from day 0 of pregnancy):** No treatment-related difference in duration of gestation (refer to Table 1 below).
- **Gestation index (live litters/pregnancies):** No treatment-related difference in live birth index or viability index (refer to Table 2 below).
- **Change in lactation:** No data
- **Changes in estrous cycles:** No data
- **Effects on sperm:** No data
- **Hematological findings incidence and severity:** Elevated platelet counts were observed for males treated with 1000 mg/kg/day during the pre-mating and pre-termination investigations. Elevated haemoglobin, erythrocyte and haematocrit counts were also evident for 1000 mg/kg/day males during the pre-mating and pre-termination investigations. Males treated with 1000 mg/kg/day also displayed elevated mean cell volume (MCV) and a reduction in mean cell haemoglobin concentration (MCHC) during the pre-mating and pre-

termination investigations. An increase in MCV was also seen for 1000 mg/kg/day females during pre-mating and terminal assessments. Although the aetiology of these changes is unclear, the level of significance achieved for haematocrit and MCHC cannot be disregarded.

No treatment-related effects were detected for animals of either sex treated with 150 or 15 mg/kg/day. The statistically significant reductions in leucocyte count, specifically in the lymphocyte fraction detected for females treated with 1000 and 150 mg/kg/day and the elevated red blood cell count detected for males treated with 15 mg/kg/day during the pre-mating assessments were minimal ($p<0.05$) and not observed at termination and were therefore considered to have arisen incidentally and not as a consequence of treatment.

- **Clinical biochemistry findings incidence and severity:** Elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and inorganic phosphorus were detected for animals of either sex with 1000 mg/kg/day during blood chemical investigations. A reduction in cholesterol and elevated bilirubin levels were also detected, with effects more prominent in the males, which also showed a slight increase in plasma urea, reduction in glucose levels and elevated albumin/globulin ratios during the pre-termination investigations.

  No such observations were detected for animals of either sex treated with 150 or 15 mg/kg/day.

  The statistically significant increase in cholesterol detected during pre-mating investigations and the reduction in aspartate aminotransferase levels detected during pre-termination investigations for males treated with 15 mg/kg/day were minimal ($p<0.05$), and in the absence of a convincing dose-related response, were considered to have arisen fortuitously. Increase in alkaline phosphatase levels detected for 150 mg/kg/day males, with no supporting evidence to suggest an effect of treatment, were considered unrelated to test material toxicity.

- **Mortality:** There were no treatment-related deaths during the study.

  A total of nine unscheduled deaths occurred during the study. One 15 mg/kg/day female was removed from the study and terminated due to uncertainty concerning its sex on Day 19. One female treated with 150 mg/kg/day was found dead on gestation Day 6. One female treated with 1000 mg/kg/day was killed *in extremis* together with the litter on gestation Day 21 and another female from this dose group was found dead on gestation Day 22. These two deaths were attributed to dystocia. The remaining deaths were most probably attributed to inappropriate dosing techniques, or the administration of an irritant test material formulation and not a toxic effect of treatment.

- **Gross pathology incidence and severity:** No treatment-related microscopic abnormalities were detected at terminal kill.

- **Clinical biochemistry findings, incidence and severity:** Elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and inorganic phosphorus were detected for animals of either sex with 1000 mg/kg/day during blood chemical investigations. A reduction in cholesterol and elevated bilirubin levels were also detected, with effects more prominent in the males, which also showed a slight increase in plasma urea, reduction in glucose levels and elevated albumin/globulin ratios during the pre-termination investigations.

No such observations were detected for animals of either sex treated with 150 or 15 mg/kg/day.

The statistically significant increase in cholesterol detected during pre-mating investigations and the reduction in aspartate aminotransferase levels detected during pre-termination investigations for males treated with 15 mg/kg/day were minimal ($p<0.05$), and in the absence of a convincing dose-related response, were considered to have arisen fortuitously. Increase in alkaline phosphatase levels detected for 150 mg/kg/day males, with no supporting evidence to suggest an effect of treatment, were considered unrelated to test material toxicity.

- **Number of implantations:** No treatment related changes in the implantation site counts were detected

- **Number of corpora lutea (recommended):** No treatment related changes in corpora lutea counts were detected

- **Ovarian primordial follicle counts:** No data

- **Organ weight changes:** Females treated with 1000 mg/kg/day showed a statistically significant increase in relative liver weight. Absolute liver weight was also elevated, but statistical significance was not achieved. An increase in absolute and relative adrenal weight was also observed for females.

  No such observations were detected for 1000 mg/kg/day males or for animals of either sex treated with 150 or 15 mg/kg/day.

  The statistically significant reduction in absolute brain weight detected for males treated with 1000 mg/kg/day was most probably attributed to the reduced bodyweight detected at this dose group and not a direct effect of treatment.

- **Histopathology incidence and severity:** The following treatment related changes were found: Lungs - Groups of alveolar macrophages were seen with a higher incidence for females treated with 1000 mg//kg/day only; Mesenteric lymph nodes - A higher incidence of sinus histiocytosis and/or foamy histiocytes, was observed in relation to treatment for animals treated with 1000 mg/kg/day but not at any other dose level; Stomach - Hyperkeratosis, frequently associated with acanthosis, was seen in the forestomach of animals of either sex treated with 1000 mg/kg/day. Focal ulceration of the forestomach epithelium was also seen for one high dose female. Treatment-related changes did not extend to the remaining treatment groups; Duodenum - Mucosal hypertrophy was seen in three males treated with 1000 mg/kg/day. A low incidence of mucosal hypertrophy was observed in all groups of females.

- **Offspring data:**

- **Litter size and weights, sex and sex ratios:** There were no treatment-related intergroup differences in litter sizes. The intergroup variability in live litter size at birth and through early lactation was not reflected in any difference in percentile pre and post implantation loss and there was no significant increase in *post partum* invariability.

- **Viability index (pups surviving 4 days/total births) and survival at 14 days:** No treatment-related difference in live birth index or viability index after 4 days (refer to Table 2 below). No data on survival at 14 days.

- **Effects on offspring:** No toxicologically significant clinical findings were observed. The clinical observations recorded for offspring throughout the dose groups were consistent with

normally expected incidence findings in pups of the age examined and were of no toxicological importance.

No treatment-related macroscopic abnormalities were detected at terminal kill. The macroscopic findings observed for interim and terminal kill offspring throughout the dose groups, were consistent with normally expected low incidence findings in pups of the age examined and, were of no toxicological importance.

- **Postnatal growth, growth rate:** No treatment-related effects were detected. A statistically significant reduction in litter weight gain was detected in offspring of females treated with 1000 mg/kg/day in comparison to controls; however this was most probably a consequence of smaller litter numbers in the high dose and in the absence of intergroup differences in mean pup weight was not considered a reproductive effect of treatment (refer to Table 3).

- **Vaginal opening (F) or preputial separation (M):** No data
- **Other observations, for instance anogenital distance, if measured:** No data
- **Organ weights:** No data

Table 1: Groups summary of Mating Performance, Fertility and Gestation Length

Dose Level (mg/kg bw/day)	No. of males paired	No. of females			Pre-Coital Interval (Days)					
		Paired	Mated	Pregnant	1	2	3	4	5	6
0 (control)	10	10	10	10	2	5	0	2	0	1
15	8	10	9	9	4	1	0	3	1	0
150	9	9	9	8	2	2	1	4	0	0
1000	9	9	9	9	3	3	1	2	0	0

Dose Level (mg/kg bw/day)	Mating Index (%)	Pregnancy Index (%)	Gestation Lengths (days)				Females with Live Offspring	Parturition Index (%)
			22	22.5	23	23.5		
0 (control)	100	100	4	5	0	1	10	100
15	90	100	4	5	0	0	9	100
150	100	89	4	3	1	0	8	100
1000	100	100	2	6	0	0	7	90

Table 2: Group Mean Litter Size, Live Birth Index and Viability Index

Dose Level (mg/kg bw/day)	No. of Litters		No. Off-spring Born	Live Offspring (post partum) Day		Sex Ratio (% Males post partum) Day		Live Birth Index (%)	Viability Index (%)
				1	4	1	4		
0 (control)	10	Mean SD	14.9 2.1	14.7 2.2	14.7 2.2	54 11	54 11	98	100
15	9	Mean SD	12.3 4.1	12.7 4.0	12.6 3.9	49 14	49 14	100	99
150	8	Mean SD	14.1 2.4	13.8 2.4	13.4 2.1	52 13	51 14	97	97
1000	7	Mean SD	13.0 1.4	13.0 1.4	12.4 1.7	55 22	55 22	100	96

Table 3: Group Mean Litter and Pup Weights

Dose Level (mg/kg bw/day)	No. of Litters		Total Litter Weight (g) Post Partum Day		Offspring Bodyweight (g) Post Partum Day	
			1	4	1	4
0 (control)	10	Mean SD	92.1 13.8	126.9 16.0	6.3 0.4	8.7 0.6
15	9	Mean SD	80.4 23.8	111.3 29.4	6.4 0.4	9.1 0.6
150	8	Mean SD	88.1 13.0	116.9 16.5	6.4 0.5	8.8 0.7
1000	7	Mean SD	81.0 8.6	**103.7 15.1	6.2 0.4	8.4 0.5

CONCLUSIONS

Remarks: The oral administration of Cashew Nutshell Liquid to rats by gavage at a maximum dose level of 1000 mg/kg/day resulted in treatment-related systemic changes in the lungs, mesenteric lymph node, stomach, and duodenum. The 'No Observed Effect Level' (NOEL) for systemic toxicity was therefore considered to be 150 mg/kg/day.
No effect of treatment was detected on reproduction or offspring development, therefore the 'No Observed Effect Level' (NOEL) for reproductive and developmental toxicity was considered to be 1000 mg/kg/day.

DATA QUALITY

- 1, Valid without restrictions

Remarks: Guideline study conducted to GLP.

REFERENCES:

Safepharm Laboratories Ltd (2005) Cashew Nutshell Liquid: Oral Gavage Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening in the Rat. SPL Project No. 661/025

OTHER:

- **Last Changed:** July 29, 2005
- **Order number for sorting:** 1

Remarks:

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201-16358C

TEST SUBSTANCE

- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)
Source: Cardolite Corporation, Lot No.: AZ-0192

METHOD

- **Method/guideline followed:** OECD TG 422
- **Test type:** Oral gavage combined repeat dose toxicity study with reproduction/developmental toxicity screening
- **GLP:** Yes
- **Year:** 2005
- **Species:** Rat
- **Strain:** Sprague-Dawley Crl:CD® (SD) IGS BR
- **Route of administration:** oral (gavage)
- **Duration of test:** Up to 49 days
- **Doses/concentration levels:** 0, 15, 150 or 1000 mg/kg bw/day
- **Sex:** male/female
- **Exposure period:** Up to 49 days
- **Frequency of treatment:** Daily
- **Control group and treatment:** Yes. Arachis oil, 4 mL/kg bw/day
- **Post exposure observation period:** none

Statistical methods:

Data were processed to give group mean values and standard deviations where appropriate.

Haematological, blood chemical, organ weight (absolute and relative to terminal bodyweight), weekly bodyweight gain, litter weights, offspring bodyweights and quantitative functional performance data were assessed for dose response relationships by linear regression analysis, followed by one way analysis of variance (ANOVA) incorporating Levene's test for homogeneity of variance. Where variances were shown to be homogenous, pairwise comparisons were conducted

using Dunnett's test. Where Levene's test showed unequal variances the data were analysed using non-parametric methods: Kruskal-Wallis ANOVA and Mann-Whitney 'U' test.

The non-parametric methods were also used to analyse implantation loss, offspring sex ratio and landmark developmental markers.

The haematology variable basophils was not analysed since consistently greater than 30% of the data were recorded as the same value.

Remarks:

- **Test subjects**

  - **Age at study initiation:** Approximately eight weeks old

  - **No. of animals/sex/dose:** 10 animals/sex/dose

- **Study Design**

  - **Vehicle:** Arachis oil BP

  - **Satellite groups and reasons they were added:** not applicable

  - **Clinical observations performed and frequency:**

    Clinical Observations: All animals were examined for overt signs of toxicity, ill-health and behavioural change immediately before and after dosing, and one and five hours after dosing, during the working week. Animals were observed immediately before and after dosing, and one hour after dosing at weekends.

    Bodyweight: Individual bodyweights were recorded on Day 0 (the day before the start of treatment) and then weekly for males until termination. Females were weighed weekly until mating was evident. Bodyweights were then recorded on Day 0, 7, 14 and 21 post coitum, and on Day 1 and 4 post partum.

    Food Consumption: During the maturation period, weekly food consumption was recorded for each cage of adults. For females showing evidence of mating, food consumption was recorded for the periods covering Days 1 - 7, 7 - 14 and 14 - 20. For females with live litters, food consumption was recorded for the period covering Days 1 to 4 post partum.

    Water Consumption: Water intake was observed daily by visual inspection of water bottles for any overt change.

  - **Functional observations performed and frequency:**

    Prior to the start of treatment and at weekly intervals for four weeks, all animals were observed for signs of functional/behavioural toxicity. Functional performance tests were also performed on five selected males and females per dose level, prior to termination, together with an assessment of sensory reactivity to difference stimuli.

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  Detailed individual clinical observations were performed for each animal using a purpose-built arena. The following parameters were observed: Gait; Tremors; Twitches; Convulsions; Bizarre/Abnormal/Stereotypic behaviour; Salivation; Pilo-erection; Exophthalmia; Lachrymation; Hyper/Hypothermia; Skin colour; Respiration; Palpebral closure; Urination; Defecation; Transfer arousal; Tail elevation.

- **Functional performance tests performed and frequency:**

  Motor Activity: Purpose-built 44 infra-red beam automated activity monitors were used to assess motor activity. Animals were randomly allocated to the activity monitors. The tests were performed at approximately the same time each day, under similar laboratory conditions. The evaluation period was one hour for each animal. The percentage of time each animal was active and mobile was recorded for the overall one hour period and also during the final 20% of the period (considered to be the asymptotic period).

  Forelimb/Hindlimb Grip Strength: An automated grip strength meter was used. Each animal was allowed to grip the proximal metal bar of the meter with its forepaws. The animal was pulled by the base of the tail until its grip was broken. The animal was drawn along the trough of the meter by the tail until its hind paws gripped the distal metal bar. The animal was pulled by the base of the tail until its grip was broken. A record of the force required to break the grip for each animal was made. Three consecutive trials were performed for each animal.

- **Sensory reactivity tests performed and frequency:**

  Each animal was individually assessed for sensory reactivity to auditory, visual and proprioceptive stimuli. The following parameters were observed: Grasp response; Vocalisation; Toe pinch; Tail pinch; Finger approach; Touch escape; Pupil reflex; Startle reflex; Blink reflex.

- **Laboratory investigations performed and frequency:**

  Hematological and blood chemical investigations were performed on five males and five females selected from each test and control group on Day 13 (day prior to pairing). Blood samples were obtained from the lateral tail vein. Blood samples were also taken prior to termination (Day 48) for five males per dose group, and during termination on Day 5 *post* partum for all females but only values for five females were reported. Animals were not fasted prior to sampling.

  Hematology: The following parameters were measured on blood collected into tubes containing potassium EDTA anti-coagulant: Hemoglobin (Hb); Erythrocyte count (RBC); Hematocrit (Hct); Erythrocyte indices (mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC)); Total leucocyte count (WBC); Differential leucocyte count (neutrophils (Neut), lymphocytes (Lymph), monocytes (Mono), eosinophils (Eos), basophils (Bas)); Platelet count (PLT). Prothrombin time (CT) and activated partial thromboplastin time (APTT) were assessed using samples collected into sodium citrate solution (0.11 mol/l).

  Blood Chemistry: The following parameters were measured on plasma from blood collected into tubes containing lithium heparin anti-coagulant: Urea; Glucose; Total

protein; Albumin; Albumin/Globulin (A/G) ratio (by calculation); sodium; potassium; chloride; calcium; Inorganic phosphorus; aspartate aminotransferase; alanine aminotransferase; alkaline phosphatase; creatinine; Total cholesterol; Total bilirubin.

- **Organs examined at necropsy (macroscopic and microscopic):**

  Surviving adult females were killed by intravenous overdose of sodium pentobarbitone followed by exanguination on Day 5 post partum. Following the termination of all adult females, all surviving males were killed by intravenous overdose of sodium pentobarbitone followed by exsanguination.

  All adult animals, including those dying during the study, were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

  Organ Weights: The following organs, removed from adult animals that were killed at the end of the study, were dissected free from fat and weighed before fixation: Adrenals; brain, Epididymides; Heart; Kidneys; Histopathology; Liver; Ovaries; Spleen; Testes; Thymus.

  Histopathology: Samples of the following tissues were preserved from five males and five females from each dose group, in buffered 10% formalin. The tissues shown in italics were also removed from the remaining animals: Adrenals; Aoarta (thoracic); Bone and bone marrow (sternum); Brain (including cerebrum, cerebellum and pons); Caecum; *Coagulating gland*; Colon; Duodenum; *Epididymides*; Eyes; Gross lesions; Heart; Ileum; Jejunum; Kidneys; Liver; Lungs (with bronchi); Lymph nodes (cervical and mesenteric);Mammary gland;Muscle (skeletal); *Ovaries*; Pancreas; *Pituitary; Prostate*; Oesophagus; Rectum; Salivary glands (submaxillary);Sciatic nerve; *Seminal vesicles*; Skin (hind limb); Spinal cord (cervical); Spleen; Stomach; Thyroid/parathyroid; Trachea; *Testes*; Thymus; Urinary bladder; *Uterus/cervix*; Vagina.

RESULTS

- **NOEL:** 150 mg/kg bw/day
- **LOEL:** 1000 mg/kg bw/day

- **Actual dose received by sex:** 0, 15, 150 or 1000 mg/kg bw/day

- Toxic response/effects by dose level: See remarks

- Statistical results, as appropriate: See remarks

Remarks:

- **Body weight:** A slightly reduced bodyweight gain was observed for 1000 mg/kg/day males during the first two weeks of the study. Reduced bodyweight gain was also observed for 1000 mg/kg/day females during the later stages of the gestation period.

- **Food/water consumption:** No adverse effect on dietary intake or food efficiency was detected. No intergroup differences in water consumption were detected.

- **Description, severity, time of onset and duration of clinical signs:** Increased salivation was detected prior to dosing and up to five hours after dosing for animals of either sex

treated with 1000 mg/kg/day from Day 9 onwards. An isolated incident of increased salivation was detected up to one hour after dosing for one male treated with 150 mg/kg/day on Day 8 only. One female treated with 150 mg/kg/day developed hunched posture, pilo-erection, tiptoe gait, red/brown staining around the mouth, laboured respiration and pallor of the extremities on Day 5 and was subsequently terminated due to the severity of these observations. On Day 39 of the study (gestation Day 21), one female treated with 1000 mg/kg/day showed staining around the vagina, hunched posture, tiptoe gait, pilo-erection, pallor of the extremities and red/brown staining around the snout. This animal had given birth to a total of sixteen pups, twelve of which were found dead. This animal, together with the live pups were subsequently terminated on humane grounds. No such observations were observed for animals of either sex treated with 15 mg/kg/day.

- **Behavioural Assessment:** Increased salivation was detected for individual animals of either sex treated with 1000 mg/kg/day during the Week 3 and Week 4 assessments. This observation was also observed for two 1000 mg/kg/day males during the post-mating assessments and for one 1000 mg/kg/day female during the Day 4 *post partum* assessments. No such effects were detected for animals of either sex treated with 150 or 15 mg/kg/day. All remaining inter and intra group differences in urination, defecation and transfer arousal scores were considered to be a result of normal variation for rats of the strain and age used and were of no toxicological importance.

- **Functional Performance Tests:** There were no treatment-related changes in the functional performance parameters measured. Statistical analysis of the data revealed no significant intergroup differences.

- **Sensory Reactivity Assessments:** There were no treatment-related changes in sensory reactivity. All inter and intra group differences in sensory reactivity scores were considered to be a result of normal variation for rats of the strain and age used and were of no toxicological importance.

- **Ophthalmologic findings, incidence and severity:** No data

- **Hematologic findings, incidence and severity:** Elevated platelet counts were observed for males treated with 1000 mg/kg/day during the pre-mating and pre-termination investigations. Elevated haemoglobin, erythrocyte and haematocrit counts were also evident for 1000 mg/kg/day males during the pre-mating and pre-termination investigations. Males treated with 1000 mg/kg/day also displayed elevated mean cell volume (MCV) and a reduction in mean cell haemoglobin concentration (MCHC) during the pre-mating and pre-termination investigations. An increase in MCV was also seen for 1000 mg/kg/day females during pre-mating and terminal assessments. Although the aetiology of these changes is unclear, the level of significance achieved for haematocrit and MCHC cannot be disregarded.

  No treatment-related effects were detected for animals of either sex treated with 150 or 15 mg/kg/day. The statistically significant reductions in leucocyte count, specifically in the lymphocyte fraction detected for females treated with 1000 and 150 mg/kg/day and the elevated red blood cell count detected for males treated with 15 mg/kg/day during the pre-mating assessments were minimal ($p<0.05$) and not observed at termination and were therefore considered to have arisen incidentally and not as a consequence of treatment.

- **Clinical biochemistry findings, incidence and severity:** Elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and inorganic

phosphorus were detected for animals of either sex with 1000 mg/kg/day during blood chemical investigations. A reduction in cholesterol and elevated bilirubin levels were also detected, with effects more prominent in the males, which also showed a slight increase in plasma urea, reduction in glucose levels and elevated albumin/globulin ratios during the pre-termination investigations.

No such observations were detected for animals of either sex treated with 150 or 15 mg/kg/day.

The statistically significant increase in cholesterol detected during pre-mating investigations and the reduction in aspartate aminotransferase levels detected during pre-termination investigations for males treated with 15 mg/kg/day were minimal ($p<0.05$), and in the absence of a convincing dose-related response, were considered to have arisen fortuitously. Increase in alkaline phosphatase levels detected for 150 mg/kg/day males, with no supporting evidence to suggest an effect of treatment, were considered unrelated to test material toxicity.

- **Mortality and time to death:** There were no treatment-related deaths during the study.

  A total of nine unscheduled deaths occurred during the study. One 15 mg/kg/day female was removed from the study and terminated due to uncertainty concerning its sex on Day 19. One female treated with 150 mg/kg/day was found dead on gestation Day 6. One female treated with 1000 mg/kg/day was killed *in extremis* together with the litter on gestation Day 21 and another female from this dose group was found dead on gestation Day 22. These two deaths were attributed to dystocia. The remaining deaths were most probably attributed to inappropriate dosing techniques, or the administration of an irritant test material formulation and not a toxic effect of treatment.

- **Gross pathology incidence and severity:** No treatment-related microscopic abnormalities were detected at terminal kill.

- **Organ weight changes:** Females treated with 1000 mg/kg/day showed a statistically significant increase in relative liver weight. Absolute liver weight was also elevated, but statistical significance was not achieved. An increase in absolute and relative adrenal weight was also observed for females.

  No such observations were detected for 1000 mg/kg/day males or for animals of either sex treated with 150 or 15 mg/kg/day.

  The statistically significant reduction in absolute brain weight detected for males treated with 1000 mg/kg/day was most probably attributed to the reduced bodyweight detected at this dose group and not a direct effect of treatment.

- **Histopathology incidence and severity:** The following treatment related changes were found: Lungs - Groups of alveolar macrophages were seen with a higher incidence for females treated with 1000 mg//kg/day only; Mesenteric lymph nodes - A higher incidence of sinus histiocytosis and/or foamy histiocytes, was observed in relation to treatment for animals treated with 1000 mg/kg/day but not at any other dose level; Stomach - Hyperkeratosis, frequently associated with acanthosis, was seen in the forestomach of animals of either sex treated with 1000 mg/kg/day. Focal ulceration of the forestomach epithelium was also seen for one high dose female. Treatment-related changes did not extend to the remaining treatment groups; Duodenum - Mucosal hypertrophy was seen in

three males treated with 1000 mg/kg/day. A low incidence of mucosal hypertrophy was observed in all groups of females.

CONCLUSIONS

Remarks: The oral administration of Cashew Nutshell Liquid to rats by gavage at a maximum dose level of 1000 mg/kg/day resulted in treatment-related systemic changes in the lungs, mesenteric lymph node, stomach, and duodenum. The 'No Observed Effect Level' (NOEL) for systemic toxicity was therefore considered to be 150 mg/kg/day.

DATA QUALITY

- 1, Valid without restrictions

Remarks: Guideline study conducted to GLP.

REFERENCES:

Safepharm Laboratories Ltd (2005) Cashew Nutshell Liquid: Oral Gavage Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening in the Rat. SPL Project No. 661/025

OTHER:

- **Last Changed:** July 29, 2005
- **Order number for sorting:** 1

Remarks:

HUMAN HEALTH ENDPOINTS
13.0 ACUTE TOXICITY

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201-16358D

TEST SUBSTANCE

- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)
Source: Cardolite Corporation, Lot No.: AZ-0192

METHOD

- **Method:** Range-finding study for OECD 422
- **Test Type:** 14-day repeat dose range-finder
- **GLP:** Yes
- **Year:** 2005
- **Species/strain:** Rat, Sprague-Dawley
- **Sex:** Male/female
- **No. of animals/sex/dose:** 3 animals/sex/dose
- **Vehicle:** Arachis oil
- **Route of administration:** Oral (gavage)

Remarks:

- **Age:** not given. Males weighed 255-300 g, females 179-219 g.
- **Doses:** 0, 1000 mg/kg bw/day for 14 days
- **Volume administered:** 4 mL/kg
- **Post dose observation period:** none

RESULTS

- **LD50:** The LD50 is likely to be greater than 1000 mg/kg.
- **Number of deaths at each dose level:** No unscheduled deaths occurred during the 14 day treatment period.

Remarks:

- **Time of death:** not applicable
- **Clinical signs at each dose level:** No clinically observable signs of toxicity were detected. Increased salivation was detected up to 10 minutes after dosing for males treated with 1000 mg/kg bw/day from day 3 and for 1000 mg/kg bw/day females from day 5 onwards, with an isolated incident of increased salivation detected prior to dosing for one male treated with 1000 mg/kg/day. This observation is often recorded following the oral administration of an unpleasant and/or locally irritant test material formulation and in isolation is not considered to be indicative of systemic toxicity.

- **Bodyweight:** A slight reduction in bodyweight gain was observed for animals treated with 1000 mg/kg bw/day in comparison to controls during the rangefinder, with individual bodyweight losses observed for one male at day 4, another male at Day 11 and one female on Day 14.

- **Necropsy findings:** No macroscopic abnormalities were detected for test or control animals at terminal kill.

CONCLUSIONS

Remarks: The LD50 is likely to be greater than 1000 mg/kg.

DATA QUALITY

- 2, Valid with restrictions

Remarks: Range-finder for repeat dose toxicity study, conducted to GLP.

REFERENCES:

Safepharm Laboratories Ltd (2005) Cashew Nutshell Liquid: Oral Gavage Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening in the Rat. SPL Project No. 661/025

OTHER:

- **Last Changed:** August 05, 2005
- **Order number for sorting:** 1

Remarks:

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201-16358E

TEST SUBSTANCE

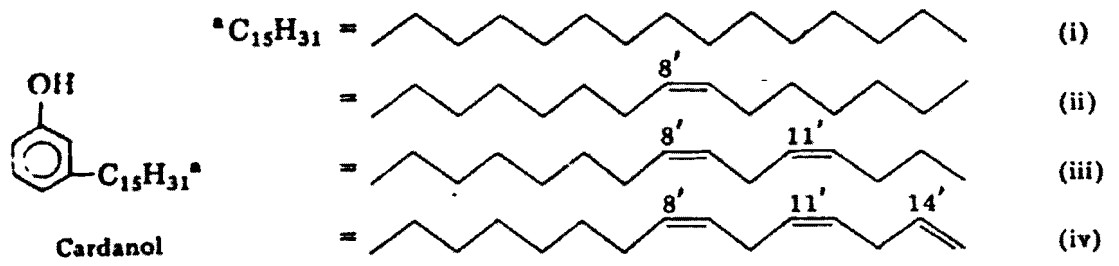
- Cashew Nutshell Liquid

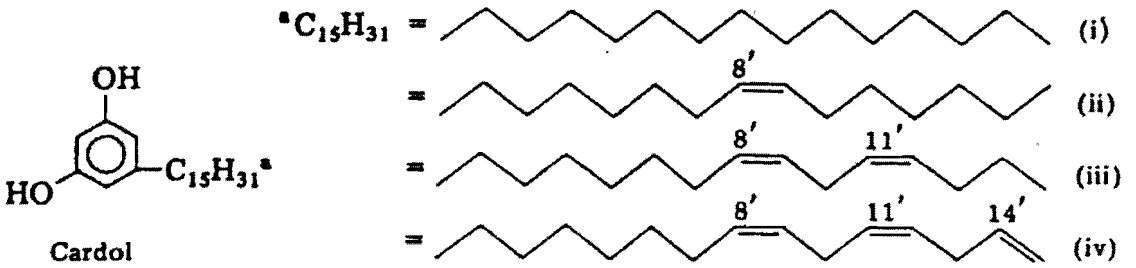
Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)

Typically, the composition of technical CNSL is approximately 52% cardanol, 10% cardol, 30% polymeric material, with the remainder being made up of other substances.

The technical CNSL is often further processed by distillation at reduced pressure to remove the polymeric material. The composition of distilled technical CNSL is approximately 78% cardanol, 8% cardol, 2% polymeric material, < 1% 2-methyl cardanol, 2.3% heptadecyl homologue triene, 3.8% heptadecyl homologue diene and the remainder other homologous phenols.

For the purposes of fulfilling this endpoint, calculations will be limited to cardanol and cardol. Each of these substances consists of mixtures of components having various degrees of unsaturation in the alkyl side-chain (see below). Calculations were performed for each component.





METHOD

- **Test:** Level III Fugacity Model
- **Method:** Calculated using Epiwin v3.12 Level III Fugacity Model
- **Year:** 2005
- **GLP:** No

Remarks

RESULTS

Cardanol (i)

```
Molecular Wt: 304.52
Henry's LC  : 9.74e-005 atm-m3/mole (Henrywin program)
Vapor Press : 1.27e-006 mm Hg  (Mpbpwin program)
Liquid VP   : 1.82e-005 mm Hg  (super-cooled)
Melting Pt  : 142 deg C (Mpbpwin program)
Log Kow     : 8.94  (Kowwin program)
Soil Koc    : 3.57e+008  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	27.3	0	0	0.09
In water	1.85	5.2	0	3.75
In soil	37.3	0	100	28
In sediment	33.5	94.8	0	68.1

Cardanol (ii)

```
Molecular Wt: 302.5
Henry's LC  : 2.56e-005 atm-m3/mole (Henrywin program)
Vapor Press : 1.24e-007 mm Hg  (Mpbpwin program)
Liquid VP   : 1.77e-006 mm Hg  (super-cooled)
Melting Pt  : 142 deg C (Mpbpwin program)
Log Kow     : 8.72  (Kowwin program)
Soil Koc    : 2.15e+008  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	7.1	0	0	0.03
In water	1.3	5.2	0	3.75
In soil	67.8	0	100	28.2
In sediment	23.7	94.8	0	68

Cardanol (iii)

```
Molecular Wt: 300.49
Henry's LC  : 6.74e-006 atm-m3/mole (Henrywin program)
Vapor Press : 1e-007 mm Hg  (Mpbpwin program)
Liquid VP   : 1.41e-006 mm Hg  (super-cooled)
Melting Pt  : 141 deg C (Mpbpwin program)
Log Kow     : 8.51  (Kowwin program)
Soil Koc    : 1.33e+008  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	6.2	0	0	0.02
In water	1.3	5.2	0	3.75
In soil	69.2	0	100	28.2
In sediment	23.3	94.8	0	68.1

Cardanol (iv)

```
Molecular Wt: 298.47
Henry's LC  : 2.13e-006 atm-m3/mole (Henrywin program)
Vapor Press : 1.08e-007 mm Hg  (Mpbpwin program)
Liquid VP   : 1.5e-006 mm Hg  (super-cooled)
Melting Pt  : 140 deg C (Mpbpwin program)
```

```
Log Kow     : 8.37  (Kowwin program)
Soil Koc    : 9.61e+007  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	2.55	0	0	0
In water	0.68	2.66	0	1.91
In soil	71.8	0	99.9	28.1
In sediment	25	97.3	0.07	69.9

Cardol (i)

```
Molecular Wt: 320.52
Henry's LC  : 1.2e-008 atm-m3/mole (Henrywin program)
Vapor Press : 1.9e-009 mm Hg  (Mpbpwin program)
Liquid VP   : 5.24e-008 mm Hg  (super-cooled)
Melting Pt  : 171 deg C (Mpbpwin program)
Log Kow     : 8.46  (Kowwin program)
Soil Koc    : 1.18e+008  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	2.05	0	0	0.04
In water	1.14	5.2	0	3.71
In soil	76.2	0	100	29
In sediment	20.7	94.8	0	67.3

Cardol (ii)

```
Molecular Wt: 318.5
Henry's LC  : 3.15e-009 atm-m3/mole (Henrywin program)
Vapor Press : 1.48e-009 mm Hg  (Mpbpwin program)
Liquid VP   : 4.14e-008 mm Hg  (super-cooled)
Melting Pt  : 171 deg C (Mpbpwin program)
Log Kow     : 8.24  (Kowwin program)
Soil Koc    : 7.12e+007  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	1.3	0	0	0.02
In water	1.1	5.2	0	3.73
In soil	76.8	0	100	28.9
In sediment	20.8	94.8	0	67.3

Cardol (iii)

```
Molecular Wt: 316.49
Henry's LC  : 8.29e-010 atm-m3/mole (Henrywin program)
Vapor Press : 1.15e-009 mm Hg  (Mpbpwin program)
Liquid VP   : 3.27e-008 mm Hg  (super-cooled)
Melting Pt  : 172 deg C (Mpbpwin program)
Log Kow     : 8.03  (Kowwin program)
Soil Koc    : 4.39e+007  (calc by model)
```

	1000 kg/h emission to these compartments separately	Simultaneous 1000 kg/h emission to air, water and soil compartments

	Air	Water	Soil	
In air	0.625	0	0	0.02
In water	1.16	5.3	0	3.73
In soil	77.3	0	100	29.3
In sediment	20.9	94.7	0	66.9

Cardol (iv)

```
Molecular Wt: 314.47
Henry's LC  : 2.62e-010 atm-m3/mole (Henrywin program)
Vapor Press : 1.24e-009 mm Hg  (Mpbpwin program)
Liquid VP   : 3.46e-008 mm Hg  (super-cooled)
Melting Pt  : 171 deg C (Mpbpwin program)
Log Kow     : 7.89  (Kowwin program)
Soil Koc    : 3.18e+007  (calc by model)
```

	1000 kg/h emission to these compartments separately			Simultaneous 1000 kg/h emission to air, water and soil compartments
	Air	Water	Soil	
In air	0.0888	0	0	0
In water	0.597	2.69	0	1.86
In soil	77.7	0	100	30.9
In sediment	21.6	97.3	0	67.2

CONCLUSIONS

Based on the estimations as a whole, the major components of cashew nutshell liquid will distribute mainly to soil (37.3 - 77.7%) if released to the air compartment, almost exclusively to sediment (94.8 – 97.3%) if released to water, exclusively to soil if released to soil and mainly to sediment (66.9 – 69.9%) if released simultaneously to all air, soil and water compartments.

DATA QUALITY

- **Reliabilities:** 2, valid with restrictions

REFERENCES (Free Text)

Safepharm Laboratories Ltd (2005) Cashew Nutshell Liquid: Epiwin v3.12 Calculations.

OTHER

- **Last changed:** August 05, 2005
- **Order number for sorting:** 1

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TEST SUBSTANCE

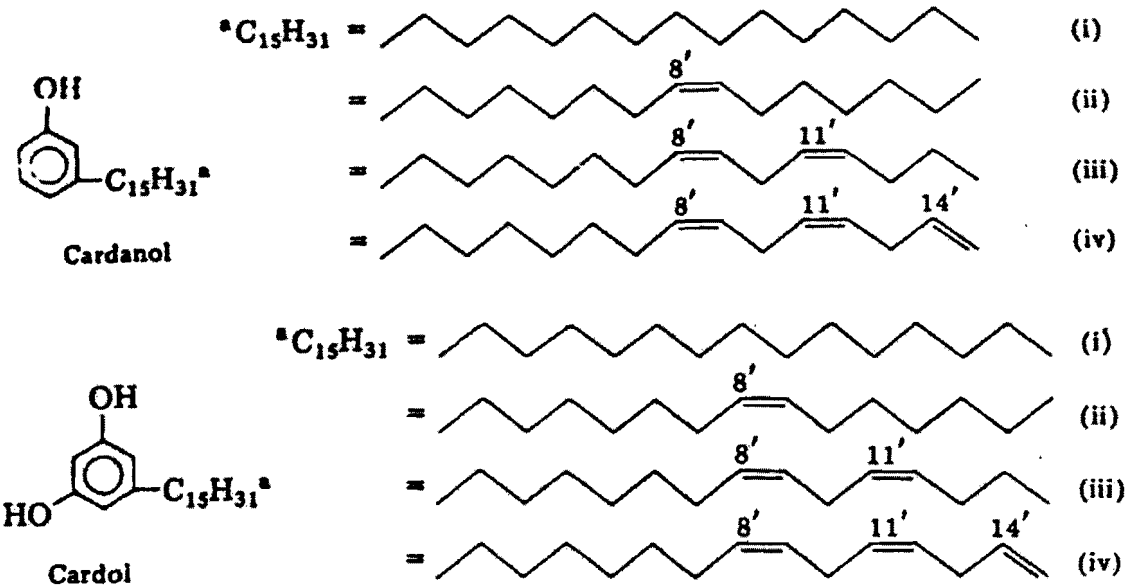
- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)

Typically, the composition of technical CNSL is approximately 52% cardanol, 10% cardol, 30% polymeric material, with the remainder being made up of other substances.

The technical CNSL is often further processed by distillation at reduced pressure to remove the polymeric material. The composition of distilled technical CNSL is approximately 78% cardanol, 8% cardol, 2% polymeric material, < 1% 2-methyl cardanol, 2.3% heptadecyl homologue triene, 3.8% heptadecyl homologue diene and the remainder other homologous phenols.

For the purposes of fulfilling this endpoint, calculations will be limited to cardanol and cardol. Each of these substances consists of mixtures of components having various degrees of unsaturation in the alkyl side-chain (see below). Calculations were performed for each component.



METHOD

- **Method:** Calculated using AOPWIN v1.91
- **GLP:** No
- **Year:** 2003

RESULTS

- **Indirect photolysis**

- **Sensitizer:** OH radicals
- **Concentration of sensitizer:** 1.5E+06 OH/cm^3
- **Rate constant:** See Table
- **Half-life:** See Table

Component	Rate constant (cm3/molecule-sec)	Half life (hrs)
Cardanol (i)	102.3748 E-12	1.254
Cardanol (ii)	155.4202 E-12 [Cis-isomer] 163.0202 E-12 [Trans-isomer]	0.826 [Cis-isomer] 0.787 [Trans-isomer]
Cardanol (iii)	208.5151 E-12 [Cis-isomer] 223.7151 E-12 [Trans-isomer]	0.616 [Cis-isomer] 0.574 [Trans-isomer]
Cardanol (iv)	233.2842 E-12 [Cis-isomer] 248.4842 E-12 [Trans-isomer]	0.550 [Cis-isomer] 0.517 [Trans-isomer]
Cardol (i)	219.7015 E-12	0.584
Cardol (ii)	272.7469 E-12 [Cis-isomer] 280.3470 E-12 [Trans-isomer]	0.47 [Cis-isomer] 0.458 [Trans-isomer]
Cardol (iii)	325.8418 E-12 [Cis-isomer] 341.0418 E-12 [Trans-isomer]	0.394 [Cis-isomer] 0.376 [Trans-isomer]
Cardol (iv)	350.6109 E-12 [Cis-isomer] 365.8109 E-12 [Trans-isomer]	0.366 [Cis-isomer] 0.351 [Trans-isomer]

CONCLUSIONS

Indirect photo-oxidation by hydroxy radicals (1500000 molecule/cm^3) is predicted to occur with a half-life estimated at 0.351-1.254 hrs (calculated using AOPWIN v1.91 at 25 °C, rate constant, 102.3748 – 365.8109 E-12 cm^3/molecule/sec, 12-hour day).

DATA QUALITY

- **Reliabilities:** 2, valid with restrictions

REFERENCES (Free Text)

Safepharm Laboratories Ltd (2005) Cashew Nutshell Liquid: Epiwin v3.12 Calculations.

OTHER

- **Last changed:** August 05, 2005
- **Order number for sorting:** 1

PHYSICAL/CHEMICAL ELEMENTS
5.0 WATER SOLUBILITY

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201-16358G

TEST SUBSTANCE

- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)
Source: Cardolite Corporation, Lot No.: AZ-0192

METHOD

- **Method/guideline:** OECD TG105, OPPTS 830.7840
- **GLP:** Yes
- **Year:** 2004

Remarks: The determination was carried out using the flask method.

RESULTS

- **Solubility:** 3.05×10^{-4} g/l of solution
- **Temperature °C:** 20

Remarks: The preliminary water solubility test indicated that the column elution method should have been performed as the solubility was less than 1×10^{-2} g/l. However, due to the physical nature of the test material, it was not possible to use this method; experience has shown that liquid test materials coated onto glass beads cause these beads to adhere together forming a plug within the column and thus preventing water circulation.

CONCLUSIONS

Remarks: The water solubility of the test material has been determined to be 3.05×10^{-4} g/l of solution at 20.0 ± 0.5°C.

DATA QUALITY

- **Reliabilities:** 1, Valid without restrictions

Remarks: Guideline study conducted to GLP

REFERENCES (Free Text)

Safepharm Laboratories Ltd (2004) Cashew Nutshell Liquid: Determination of Water Solubility and Partition Coefficient. Data Requirements: OECD Guidelines for Testing of Chemicals US EPA Office of Prevention, Pesticides and Toxic Substances, Series 830: Product Properties Test Guidelines. SPL Project No. 661/024

OTHER

- **Last Changed:** July 27, 2005
- **Order number for sorting:** 1
- **Remarks:**

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PHYSICAL/CHEMICAL ELEMENTS
4.0 PARTITION COEFFICIENT

201-16358H

TEST SUBSTANCE

- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)
Source: Cardolite Corporation, Lot No.: AZ-0192

METHOD

- **Method/guideline:** OECD TG117, OPPTS 830.7570
- **GLP:** Yes
- **Year:** 2004

Remarks: The determination was carried out using the HPLC Method

RESULTS

- **Log Pow:** >6.20
- **Temperature °C:**

Remarks: The three peaks obtained in the sample chromatography were confirmed as test material using the gas chromatography conditions used in the water solubility test. The mobile phase was unadjusted as the test material contained no modes of dissociation within range and scope of the method (pH 5 to 9).

CONCLUSIONS

Remarks: The partition coefficient of all components of the test material have been determined to be >1.59 x 10^6, $\log_{10} P_{ow}$ >6.20.

DATA QUALITY

- **Reliabilities:** 1, Valid without restrictions

Remarks: Guideline study conducted to GLP

REFERENCES (Free Text)

Safepharm Laboratories Ltd (2004) Cashew Nutshell Liquid: Determination of Water Solubility and Partition Coefficient. Data Requirements: OECD Guidelines for Testing of Chemicals US EPA Office of Prevention, Pesticides and Toxic Substances, Series 830: Product Properties Test Guidelines. SPL Project No. 661/024

OTHER

- **Last Changed:** July 27, 2005
- **Order number for sorting:** 1

Remarks:

PHYSICAL/CHEMICAL ELEMENTS
3. VAPOUR PRESSURE

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201-16358I

TEST SUBSTANCE

- Cashew Nutshell Liquid

Remarks: Test substance: Cashew nut shell liquid (CAS # 8007-24-7)
Source: Cardolite Corporation, Lot No.: AZ-0192

METHOD

- Method/guideline: OECD TG104, OPPTS 830.7950
- GLP: Yes
- Year: 2004

Remarks: The vapour pressure was determined using a vapour pressure balance system with measurements being made at several temperatures and linear regression analysis used to calculate the vapour pressure at 25 °C.

RESULTS

- **Vapour pressure value:** 5.0×10^{-5} Pa
- **Temperature °C:** 25
- **Decomposition:** No

Remarks:

CONCLUSIONS

Remarks:

DATA QUALITY

- 1, Valid without restrictions

Remarks: Guideline study conducted to GLP

REFERENCES (Free Text)

Safepharm Laboratories Ltd (2004) Cashew Nutshell Liquid: Determination of Vapour Pressure. Data Requirements: OECD 104, OPPTS 830.7950. SPL Project No. 661/023

OTHER

- **Last Changed:** July 27, 2005
- **Order number for sorting:** 1

Remarks: