CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
N,N-Bis(3-aminopropyl)laurylamine

Chemical Code # 6115, Document Processing Number (DPN) # 53209
SB 950 # NA
3/7/14

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No study submitted *
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No study submitted*
Reproduction, rat:	No data gap, possible adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	Data gap
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No study submitted*

Toxicology one-liners are attached.

All record numbers for the above study types through 271763 (Document No. 53209-0010) were examined. This includes all relevant studies indexed by DPR as of 3/7/14.

* The active ingredient is being evaluated for use as an antimicrobial for application to non-food-use surfaces. These toxicity studies are not required as specified under section 158.2230 in 40 CFR (2013).

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T140307
Revised by T. Moore, 3/7/14

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

53209-0010; 271761; "P4198:Toxicokinetic Study in the Rat"; (A.B. McEwen; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. LZA 103\961230; 9/5/96); This study comprised three components, excretion balance, plasma kinetics and tissue distribution assessment. In the excretion balance study, 4 Sprague-Dawley rats/sex/group were dosed orally by gavage with 3 or 30 mg/kg of ^{14}C-P4198 (N,N-bis-(3-aminopropyl)dodecylamine) (code no. LZA/104/54, specific activity: 65.8 uCi/mg, radiochemical purity: $\geq$ 97%). Urine and feces were collected at specified intervals up to 120 hours post-dose. Expired air was trapped up to 48 hours post-dose. In the plasma kinetics study, 9 animals/sex/group were dosed with 3 or 30 mg/kg of the test material and blood was drawn from the tail vein of 3 animals/sex/group/time point at specified times up to 168 hours post-dose. In the tissue distribution assessment, 5 males were dosed orally with 3 mg/kg of the test material and one animal per time point was euthanized at 3, 6, 24, 48 and 120 hours post-dose. Whole body autoradiographs of each animal were prepared. In the excretion recovery, 90 to 97% of the administered radiolabel was recovered in the feces. Less than 0.2% of the administered dose was recovered in the urine. One tenth to 0.4% of the radiolabel was recovered from the expired air. For the males, 93 to 95% of the administered dose was excreted within the first 48 hours, irregardless of the treatment level. For the females, 83 to 87% of the dose was excreted in the first 48 hours. Isolation and identification of metabolites in the fecal extracts was undertaken. Thin layer chromatographic analysis of the pooled samples from the 0 to 48-hour collection was performed. The only two components which were identified were the parent compound and dodecylamine. These constituted only 13 to 15% of the administered dose in the 3 mg/kg treatment group and 8 to 12% of the administered dose in the 30 mg/kg treatment group. In the plasma kinetics study, the concentration of the radiolabel in the plasma of the 3 mg/kg treatment group was below the limits of quantification. For the 30 mg/kg group, the Cmax for both males and females was 0.12 ug equivalents/ml. The time to Cmax was 12 hours. In the excretion of the radiolabel, the terminal half lives were 28.5 hours for the males and 46.3 hours for the females. Qualitatively, the whole body autoradiography demonstrated that the radiolabel was largely present in the gastrointestinal tract and its contents. **Supplemental study** (data were not sufficient to ascertain how much of the test material was absorbed and only a small fraction of the isolated components in the feces were identified structurally). (Moore, 12/31/13)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

53209-0006; 271729; "P4150: Acute Oral Toxicity in the Rat: Project Number: 102/17"; (J.R. Jones; Safepharm Laboratories Ltd., Derby, DE1 2BT, U.K.; Project No. 102/47; 1/5/88); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 250, 500, 1000 or 2000 mg/kg of P4150 (Lonzabac 12) (batch no. 130787; a.i.: 90.0%). The mortality was as follows: 250 (M/F: 0/5), 500 (M/F: 0/5), 1000 (M: 3/5, F: 4/5), 2000 (M/F: 5.5). Clinical signs included hunched posture, piloerection, lethargy, decreased respiratory rate, increased salivation and pallor of the extremities. Among the animals dying during the observation period, lesions included abnormally red lungs, dark livers and kidneys, hemorrhage in the gastric mucosa, and congestion in the small and large intestines. The necropsy examination did not reveal any treatment-related lesions in the animals surviving to the termination of the study. LD50 (95% confidence interval): (M) 933 (664 to 1310) mg/kg, (F) 812 (616 to 1072) mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 11/5/13)

Acute dermal toxicity

53209-0006; 271730; "P4150: Acute Dermal Toxicity (Limit Test) in the Rat: Project Number: 102/48"; (J.R. Jones; Safepharm Laboratories Ltd., Derby, DE1 2BT, U.K.; Project No. 102/48; 8/3/89); The skin of 5 Sprage-Dawley rats/sex was exposed to 2000 mg/kg of P4150 (Lonzabac 12) (batch no. 130787; a.i.: 90.0%) for 24 hours under an occlusive wrap. No mortality resulted from the treatment. Clinical signs included hunched posture, piloerection, and lethargy. Dermal irritation was noted at the site of application. No lesions were evident in the gross examination except for scabs at the site of application. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 11/5/13)

Acute inhalation toxicity, rat

53209-0006; 271731; "Acute Inhalation Toxicity Study in Rats-Limit Test with Lonzabac 12"; (J. Durando; Eurofins Product Safety Laboratories, Dayton, NJ; Study No. 22102; 10/23/07); Five Sprague-Dawley rats/sex were exposed nose-only to 0.053 mg/l (gravimetric) of Lonzabac 12 (batch no. DEGE914640; a.i.: 91.8%) for 4 hours. The mean MMAD (GSD) was 2.15 (2.03) um. One female died two days after exposure. Clinical signs included hypoactivity, hunched posture, dry rales and abnormal respiration. Necropsy examination of the animal which died revealed discolored lungs and discolored and distended intestines. No treatment-related lesions were evident in the necropsy examination of those animals which survived the observation period. LC50 (M/F) > 0.053 mg/l; Toxicity Category II; **Study acceptable.** (Moore, 11/6/13)

Primary eye irritation, rabbit

No study submitted.

Primary dermal irritation

53209-0006; 271732; "P4150: Acute Dermal Irritation/Corrosion Test in the Rabbit: Project Number: 102/18"; (J.R. Jones; Safepharm Laboratories Ltd., Derby, DE1 2BT, U.K.; Project No. 102/18; 1/9/88); The skin of 6 New Zealand White rabbits was treated with 0.5 ml/site, one site/animal of P4150 (Lonzabac 12) (batch no. 130787; a.i.: 90.0%) for 4 hours under a semi-occlusive wrap. Erythema, grade 4, was noted for all of the animals at 1 hour post-exposure through 7 days. At that time the study was terminated. Edema, grades 4 (2/6) and 3 (4/6), was noted at 1 hour post-exposure, diminishing to grades 3 (3/6) and 2 (3/6) at 24 hours, grade 2 (6/6) at 48 hours, grades 2 (3/6) and 1 (3/6) at 72 hours and clearing by 7 days. Blanching and blood stained tissue with scabbing noted at the treatment site. Toxicity Category I; **Study acceptable.** (Moore, 11/6/13)

53209-0006; 271733; "P4198: Acute Dermal Irritation Test in the Rabbit: Project Number: 102/177"; (J.R. Jones; Safepharm Laboratories Ltd., Derby, DE1 2BT, U.K.; Project No. 102/177; 7/6/94); The skin of 3 New Zealand White rabbits was treated with 0.5 ml/site, one site/animal of a 90% preparation of Lonzabac 12) (batch no. E06215035; a.i.: 81%) for 3 minutes under a semi-occlusive wrap. Erythema, grade 2 (3/3), was noted at 1 hour post-exposure, increasing to grade 4 in two animals with the third animal suffering too adverse a reaction to make a reading. At 48 and 72 hours, grade 4 was noted for one animal and the reaction was too adverse to make a reading for the other two animals. At 7 days, the skin irritation was too adverse to make a reading for all three of the animals. By 14 days, the signs of erythema had resolved in two of the animals. The reaction was still too adverse to assess the erythema for the third animal. Edema, grades 3 (3/3), was noted at 1 hour, increasing to grade 4 (3/3) at 24 hours. At 48 hours, the reaction was too adverse for two of the animals, grade 3 edema was noted for the third animals. The edema for this animal diminished to grade 2 at 72 hours while the edema could not be evaluated for the other two. By 7 days, the edema could not be evaluated in any of the animals. Any signs of edema had been resolved in two of the animals by 14 days. The edema could not be evaluated in the other animal. Scar tissue and reduced fur growth was evident at the site of application 14 days post-exposure. Significant dermal irritation was evident after a 3-minute exposure to the test material; Toxicity Category I; **Study supplemental.** (Moore, 11/6/13)

Dermal sensitization

53209-0006; 271734; "P4150: Skin Sensitization in the Guinea-Pig"; (S.A. Allan; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. LZA 129/953059/SS; 1/18/96); The skin of 20 male Dunkin/Hartley guinea pigs was treated with 0.5 ml of a 1% (v/v) preparation of P4150 (Lonzabac 12) diluted in water (batch no. PN 93-12, a.i.: 30.2%) in distilled water for 6 hours, once per week for 3 weeks under an occlusive wrap, in the induction phase. In the challenge phase, two weeks after the last induction treatment, these 20 animals were exposed to 0.5 ml of a 0.5% (v/v) preparation of the test material in distilled water for 6 hours and the skin response was evaluated at 24 and 48 hours post-application. At this time, 10 naive control animals were treated in the same manner. In the induction treatment, 5 of the 20 treated animals demonstrated at least one positive response during the 3 treatments. In the challenge phase, 5 of the treated animals exhibited a positive response at 24 hours post-exposure, diminishing to 4 animals at 48 hours. Three of the 10 animals in the naïve control group demonstrated a positive response at 24 hours, diminishing to 1 animal at 48 hours. Although the responses elicited in the challenge treatment were equivocal, the test material does not appear to be a dermal sensitizer. **Study acceptable.** (Moore, 11/7/13)

SUBCHRONIC STUDIES (units of mg/kg/day unless specified)

Oral toxicity, rat:

**** 53209-0006; 271736, 271737**; "90-Day Oral Toxicity Study with "P4150" in Rats followed by a 4-Week Recovery Period"; (W.D. Korn; IBR Bioanalytisches Zentrum, D-3000 Hannover 61, Germany; Project No. 20-04-0843-90; 1/20/92); Ten Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: purified water), 5, 10, 30 or 90 mg/kg/day of P4150 (Lonzabac 12) (batch no. E06401788; a.i.: 29.8%, diluted with water) for 13 weeks. A recovery cohort of 10 animals/sex/group were included in the control and 90 mg/kg groups and were retained without treatment for an additional four weeks. Two males and 3 females in the 90 mg/kg treatment group died due to misdosing during the study. The mean body weight gain of both sexes in the 30 and 90 mg/kg groups were less than that of the control group during the treatment period (NS, $p<0.05$). The food consumption of both sexes in the 90 mg/kg treatment group was less than that of the control group during the treatment period (NS, $p<0.05$). No treatment-related

effect was noted in the hematological evaluation. Although values for various clinical chemical parameters of the 90 mg/kg treatment group were significantly different from those of the control group after either 13 weeks of treatment and/or the 4-week recovery period, there were no consistent responses which demonstrated a treatment-related effect. In the urinalysis, blood was apparent in the urine of the 5 mg/kg animals and above after 13 weeks of treatment. In the recovery cohort, blood was observed in the urine of both the control and 90 mg/kg groups. The ophthalmological examination did not reveal any treatment-related ocular effects. In the necropsy examination, the mean relative kidney weights of both sexes in the 90 mg/kg group were greater than the control group at the termination of treatment and at the end of the recovery period ($p<0.05$). The mean relative adrenal, lung and testes weights of the 90 mg/kg group males were greater than the control values at both the termination of the treatment and at the end of the recovery period ($p<0.05$). The relative lung weight of the 90 mg/kg females was greater than the control at the termination of the treatment ($p<0.05$). In the histopathological examination, tubulonephrosis was noted in the kidneys of both sexes in the 90 mg/kg group at the termination of treatment, progressing to glomerulo/tubulonephrosis in the males by the end of the recovery period. Loaded macrophages were identified in the mesenteric lymph nodes of both sexes in the 30 and 90 mg/kg groups after 13 weeks of treatment and persisted in the 90 mg/kg group after the recovery period. In the nasopharyngeal tissue, epithelial cell proliferation progressing to squamous cell metaplasia was evident in both sexes of the 10, 30 and 90 mg/kg groups at the termination of the treatment. Squamous cell metaplasia was evident in only one animal at the end of the recovery period. An increased incidence of mucosal degeneration was noted in the stomach of both sexes in all of the treatment groups. The histology slides were reread by David Prentice, PCS Consultants, Ltd., per request of the study sponsor (rec. no. 271736). In his evaluation of the slides, he noted that treatment-related effects on the **kidneys** were multifocal dilatation and basophilia with evidence of degeneration, regeneration and hyperplasia in the proximal tubules. These effects were evident at the end of the treatment period. In the recovery cohort, there was active degeneration/regeneration in the proximal tubules with accompanying basophilia, abnormal epithelial nuclei and peritubular fibrosis. The effects were more severe in the 90 mg/kg males than in the females. In the respiratory portion of the **nasopharyngeal tissue**, disorganization of the epithelium with loss of goblet and ciliated cells and increased cellularity and thickness of the epithelium was noted. At higher treatment levels, inflammation, degeneration, ulceration and squamous cell metaplasia were evident. The changes persisted in the recovery cohort, with epithelial changes being adaptive and regenerative. In the **lungs**, aggregation of alveolar macrophages was noted. In some animals of the 90 mg/kg group, there was moderate inflammation accompanied by bronchiolar epithelial disruption and distention of the bronchi. In the **small intestine and mesenteric lymph nodes**, foamy macrophages were evident within the mucosa of the jejunum and in the lymph nodes. These effects persisted in the recovery cohort. Extramedullary hematopoiesis was noted in the **liver** of the 90 mg/kg females. Prentice reported that identified effects in the **stomach** were actually artifactual. **Possible adverse effect:** degeneration and fibrosis in the proximal tubules of the kidney. **Rat Subchronic Oral Toxicity NOEL:** (M/F) 5 mg/kg/day (based upon the incidence of epithelial cell proliferation and squamous cell metaplasia in the nasopharyngeal tissue of the 10 mg/kg treatment group); **Study acceptable.** (Moore, 11/12/13)

Oral toxicity, non-rodent:

No study submitted.

Dermal toxicity, 21/28-day or 90-day:

** 53209-0010; 271758; "Subchronic Dermal Toxicity/Immunotoxicity Study with Lonzabac 12 in Rats"; (W.D. Johnson; IIT Research Institute (ITTRI) Life Sciences Operation, Chicago, IL; Project ID No. 1076 SN3; 4/11/00); The protocol for this study included both immunotoxicity and subchronic dermal toxicity studies. In the immunotoxicity component, the skin of 8 Sprague-Dawley rats/sex/group was exposed to 0, 5, 10 or 20 mg/kg/day of Lonzabac 12 (Lot no. 90024; a.i.: 29.3% in water) for 6 hours/day, 5 days/week for 7 weeks (Cohort I). For the subchronic dermal toxicity portion (Cohort II), the skin of 15 rats/sex/group was exposed to the same concentrations of the test material in the same manner for 14 weeks. After the animals in the high dose group had received 3 or 4 doses at 20 mg/kg/day, treatment was suspended for 2 to 4 days due to the severity of the dermal irritation evoked by the treatment. Treatment was resumed at 15 mg/kg/day and continued for the remainder of the study. In Cohort I, one male in the control group died during the 6th week and one female in the 10 mg/kg group died during the 1st week. In Cohort II, one male in both the 10 mg/kg and the high dose groups died during the 6th week and one female each died in the 5 mg/kg, 10 mg/kg and high dose group during the 4th, 1st and 4th weeks, respectively. These deaths were deemed to be unrelated to the toxicity of the test material. The severity of the dermal erythema was evident in a dose-related manner for the three treatment groups. There was no statistically significant difference in the mean body weights of the study animals. There was no apparent treatment-related effect upon food consumption. For Cohort II, there were no physiologically significant effects upon the hematology parameters. In the clinical chemistry, the serum albumin level was reduced for the high dose females ($p<0.05$) and the serum globulin levels were increased for the 10 mg/kg and high dose females ($p<0.01$). The albumin/globulin ratio for these two groups was significantly different from that of the control group ($p<0.01$). There was no effect noted in the ophthalmological examination. In the necropsy examination, the mean absolute and relative spleen weights of the 10 mg/kg and high dose females were greater than the control values ($p<0.05$). The weights of the adrenals and thymus were not appreciably affected by the treatment. In the histopathological evaluation of the Cohort II animals, increased severity of hyperplasia, ulceration, scab formation and chronic dermal inflammation was noted at the site of application for both sexes in the 10 mg/kg and high dose groups and for the females in the 5 mg/kg group. In the axillary lymph node, increased incidence and severity of hyperplasia and accumulation of plasma cells were evident for both sexes in the 10 mg/kg and high dose groups and for the females in the 5 mg/kg group. An accumulation of macrophages was also noted in the axillary lymph node of both sexes in the high dose group. Hyperplasia in the bone marrow of the sternum was evident for both sexes in the 10 mg/kg and high dose groups and for the females in the 5 mg/kg group. In the immunotoxicity study, there was no treatment-related effect evident in the anti-SRBC antibody forming cell assay. The absolute and relative spleen weights and numbers of viable spleen cells were not affected by the treatment. The positive control was functional. **No adverse effect noted for either study. Rat Subchronic Dermal Toxicity NOEL (systemic): (M)** 5 mg/kg/day (based upon treatment-related lesions noted in the axillary lymph node and bone marrow of the males in the 10 mg/kg treatment group); **(F)** < 5 mg/kg/day (based upon the treatment-related lesions noted in the axillary lymph node and bone marrow of the 5 mg/kg females); **Localized Dermal Irritation NOEL:** (M/F) < 5 mg/kg/day (based upon the increased incidence of erythema noted over the course of the study); **Study acceptable.** (Moore, 12/27/13)

CHRONIC STUDIES

Chronic, rat

53209-0009; 271748; "Combined Chronic Toxicity and Carcinogenicity Study of N-(3-Aminopropyl)-N-Dodecylpropane-1,3-Diamine by Dietary Administration to CD® Rats, Part II: 12-Month Chronic Toxicity Study"; (J. Leuschner; LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, 21147 Hamburg, Germany; Report No. 20570/06; 10/29/10); Ten Crl:CD (SD) rats/sex/group received 0, 4, or 8 mg/kg/day of N-(3-Aminopropyl)-N-Dodecylpropane- 1,3-Diamine (batch no. 20570-M01; purity: 89.4%) in the diet for 52 weeks. An additional 20 animals/sex received 20 mg/kg/day of the test material for 52 weeks. Nine of the twenty males died prior to the termination of the study. The mean body weights of both sexes in the 20 mg/kg group were less than those of the control group over the latter course of the study (NS, p<0.01). There was no treatment-related effect on the food consumption based in the g/kg body weight/day. Although particular hematological parameters demonstrated statistical differences between the control and high dose groups at some time point during the study, there was no apparent effect attributable to the treatment. In the clinical chemistry evaluation, the serum aspartate aminotransferase activity levels were elevated for both sexes in the 20 mg/kg group and for the males in the 8 mg/kg group (p<0.01). The blood urea content was moderately increased for both sexes in the 20 mg/kg group (p<0.01). In the urinalysis, the pH values were lower for both sexes in the 20 mg/kg group. In the necropsy, the mean relative weights of the adrenals, epididymis, testes of the 20 mg/kg males were greater than those of the control group (p<0.01). The mean relative weights of the heart, kidneys and spleen of both sexes in the 20 mg/kg group were greater than the control values (p<0.01). The mean absolute kidney weights of the 20 mg/kg females were also greater than the control values (p<0.01). The myeloid/erythroid ratio in the bone marrow of the 20 mg/kg males was greater than that of the control (p<0.01). In the histopathological examination, the cellular degeneration of heart muscle was noted for both sexes of the 20 mg/kg treatment group and for the males in the 8 mg/kg group. Lympho-histiocytic infiltrations were noted in multiple tissues of both sexes in the 4 mg/kg group and above. **Possible adverse effect:** cellular degeneration of heart muscle cells; **Rat Chronic Dietary Toxicity NOEL:** (M/F) < 4 mg/kg/day (based upon the incidence of lympho-histiocytic infiltrations in multiple tissues/organs). **Study supplemental** (ophthalmological examination was not performed). (Moore, 12/17/13)

Chronic, dog

No study submitted.

Oncogenicity, rat

**** 53209-0008; 271746**; "Combined Chronic Toxicity and Carcinogenicity Study of N-(3-Aminopropyl)-N-Dodecylpropane-1,3-Diamine by Dietary Administration to CD® Rats, Part I: 104-Week Carcinogenicity Study"; (J. Leuschner; LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, 21147 Hamburg, Germany; Report No. 20570/06 (Part 1); 5/25/11); Fifty Crl:CD (SD) rats/sex received 0, 4, 8 or 20 mg/kg/day of N-(3-Aminopropyl)-N-Dodecylpropane- 1,3-Diamine (batch no. 20570-M01; purity: 89.4%) in the diet for up to 104 weeks. The initial treatment level of 20 mg/kg/day was reduced to 15 mg/kg/day on day 351 for both sexes due to excessive mortality. The treatment level was further reduced to 12 mg/kg/day on day 386 for the males and on day 407 for the females. Treatment was discontinued for the males on day 431 and on day 568 for the females. The mean body weights of both sexes in the 8 mg/kg and high dose groups were less than those of the control group over the latter course of the study (NS, p<0.01). There was no treatment-related effect on the food consumption based in the g/kg body weight/day. Although particular hematological parameters demonstrated

statistical differences between the control and high dose groups at some time point during the study, there was no apparent effect attributable to the treatment. In the clinical chemistry evaluation, the serum aspartate aminotransferase activity levels were elevated for both sexes in the high dose group and for the males in the 8 mg/kg group ($p<0.01$). The blood urea content was moderately increased for the males in the high dose group prior to their premature sacrifice. In the urinalysis, the pH values were persistently lower for both sexes in the high dose group. No treatment-related effect was noted in either the ophthalmological or auditory examinations. In the necropsy, there was no apparent treatment-related effect on the mean absolute or relative organ weights of the control, 4 and 8 mg/kg groups. The organ weights of the high dose animals could not be compared to the control weights because the high dose animals were euthanized at different time points in the study. In the histopathological examination, there were no apparent treatment-related neoplasms. Among the non-neoplastic lesions, the cellular degeneration of heart and skeletal muscle was noted for both sexes in the 4 mg/kg treatment group and above. Although other treatment-related lesions were apparent, the degeneration of muscle cells was the treatment-related effect of most concern. **Possible adverse effect:** cellular degeneration of heart and muscle cells; **Rat Chronic Dietary Toxicity NOEL:** (M/F) < 4 mg/kg/day (based upon the incidence of cell degeneration in both the heart and skeletal muscle of both sexes in the 4 mg/kg group); no neoplastic potential was demonstrated in the study. **Study acceptable.** (Moore, 12/11/13)

Oncogenicity, mouse

No study submitted.

GENOTOXICITY

Gene mutation

** 53209-0010; 271755; "Study to Determine the Ability of P4150 to Induce Mutation in Five Histidine-Requiring Strains of *Salmonella typhimurium";* (J.C. Kennelly; Microtest Research Limited, Heslington, York, Y01 5DU, United Kingdom; Study No. LOB 11/S; 2/11/88); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed for 48 hours at 37°C to P4150 (Lonzabac 12) (batch no. 130787; 30% a.i. in water) at concentrations ranging from 0.24 to 150 ug/plate w/o activation and from 0.96 to 600 ug/plate under condition of activation in the first experiment. In the second experiment, cells were exposed to concentrations of the test material ranging from 9.4 to 150 ug/plate w/o activation and from 37.5 to 600 ug/plate with activation. Each treatment level was plated in triplicate. An Aroclor-1254 induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in reverse mutations with or w/o activation. **No adverse effect indicated.** The positive controls were functional (note: no positive controls were included in the assays for strains TA1537 and TA1538 under conditions of activation). **Study acceptable.** (Moore, 12/20/13)

** 53187-0010; 271756; "**:** *In Vitro* Mammalian Cell Gene Mutation Test with P4150"; (R. Bosse; IBR Bioanalytisches Zentrum, D-3000 Hannover 61, Germany; Project No. 95-86-2077/02-90; 5/29/91); Chinese hamster V79 cells were exposed to P4150 (Lonzabac 12) (batch no. E 06210128; 29.5% of a.i. in water) at concentrations ranging from 0.05 to 5.00 ug/ml for 5 hours at 37° C with and w/o activation. Two trials were performed with single cultures for each treatment level. A rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in forward mutation was evident in the cultures with or w/o activation. **No**

adverse effect indicated. The positive controls were functional. **Study acceptable.** (Moore, 12/23/13)

Chromosome damage

** 53209-0010; 271754; "*In Vitro* Mammalian Cytogenetic Test with P4150"; (R. Bosse; **:** IBR Bioanalytisches Zentrum, D-3000 Hannover 61, Germany; Project No. 95-86-2077/02-90; 6/26/91); V79 Chinese hamster cells were exposed to concentrations of P4150 (Lonzabac 12) (batch no. E 06210128; 29.5% of a.i. in water) ranging from 0.1 to 10 ug/ml with and w/o activation for 5 hours, followed by an additional 12 or 19 hours of incubation. A rat liver S9 fraction was used to metabolize the test material. Two trials were performed with duplicate cultures per treatment level. Two hundred metaphases per culture were evaluated (400 metaphases per treatment level). The incidence of polyploidy was also determined. There was no increase in the incidence of chromosomal aberrations at all treatment levels in either the non-activated or activated assays. However, there was an increase in the incidence of polyploidy with and w/o activation. Positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 12/19/13)

DNA damage or miscellaneous effects

** 53209-0010; 271763; "*In Vivo* Mouse Micronucleus Assay with Lonzabac 12"; (G.L. Erexson; Covance Laboratories Inc., Vienna, VA; Study No. 7483-101; 7/7/04, amended, 7/27/04); Six CD-1 male mice/group/time point were treated intraperitoneally with 0 (vehicle: deionized water), 2.0, 4.0 or 8.0 mg/kg of Lonzabac 12 (lot no. 140007; purity: 90%). Five animals/group were euthanized at 24 hours post-dose. An additional 5 animals each in the control and 8 mg/kg groups were euthanized at 48 hours post-dose. A positive control group of 6 animals were treated by oral gavage with cyclophosphamide, 80 mg/kg and five animals were euthanized 24 hours post-dose. Bone marrow samples from the femur and tibia were examined and the ratio of polychromatic (PCE) to normochromatic erythrocytes (NCE) and the percentage of PCE with a micronucleus were determined. No treatment-related increase in the number of PCEs with a micronucleus was noted. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 1/2/14)

REPRODUCTIVE TOXICITY, RAT

**** 53209-0007; 271744, 271745**; "P4150: Two Generation Reproduction Study in Rats"; (S.J. Barton; Inveresk Research International, Tranent, EH33 2NE, Scotland; Project No. 490924; 3/24/95); In the F0 generation, 28 Sprague Dawley rats/sex/group were dosed orally by gavage with 0, 10, 30, or 90 mg/kg/day of P4150 (Lonzabac 12) (batch no. PN-93-12; a.i.: 30.2% in water) for a 10-week premating period, during mating and for the 3-week gestation and lactation periods. At the conclusion of the lactation period, 24 F1 pups/sex/group were selected and treated for a 11-week premating period, during mating, and for the 3 week gestation and lactation periods. In the F0 generation, two males in the control group, one male both in the 10 mg/kg and 30 mg/kg groups and 2 males in the 90 mg/kg died prematurely. For the females in the F0 generation, one animal in the 30 mg/kg group and 6 females in the 90 mg/kg group died. In the F1 generation, one female in the 10 mg/kg group and one male and two females in the 90 mg/kg group died during the study. The parents in both generations of the 90 mg/kg treatment group demonstrated clinical signs of dyspnea, hunched posture/piloerection/subdued behavior and salivation. The mean body weight gains of the both sexes in the 90 mg/kg treatment group for both generations were less than those of the control during the premating period and for the females during the gestation period. There was no apparent treatment-related effect on the fertility or gestation indices. The viability indices of the F2 pups in the 30 and 90 mg/kg treatment groups were less than that of the control group. **Possible adverse effect:** reduced

viability indices for the F2 pups; **Parental NOEL:** (M/F) 30 mg/kg/day (based upon clinical signs, lower mean body weight gain, and increased mortality demonstrated by both sexes in the 90 mg/kg treatment group), **Reproduction NOEL:** 90 mg/kg/day (based upon the lack of a treatment-related effect at the highest treatment level), **Developmental NOEL:** 10 mg/kg/day (based upon lower viability index for the F2 generation pups of the 30 mg/kg treatment group); **Study acceptable.** (Moore, 12/3/13)

DEVELOPMENTAL TOXICITY

Rat

** 53209-0007; 271742; "P4150: Developmental Toxicity Study in Rats"; (S.J. Barton; Inveresk Research International, Tranent, EH33 2NE, Scotland; Project No. 490730; 5/16/94); Twenty five mated female Sprague-Dawley/group were dosed orally by gavage with 0, 25, 75 or 200 mg/kg/day of P4150 (Lonzabac 12) (batch no. PN-93-12; a.i.: 90%) from gestation day 6 through 16. Two dams in the 200 mg/kg group died during the study. The mean body weight gains of the dams in the 75 and 200 mg/kg groups were less than that of the control group during the treatment period (NS, $p<0.01$). The mean food consumption of these two groups was likewise less than that of the control group over the same time period ($p<0.01$). The dams in these two groups demonstrated clinical signs of salivation, dyspnea, piloerection and a hunched/subdued/cold/pale demeanor in a dose-related manner. There was no apparent treatment-related effect upon the fetuses. **No adverse effect evident. Maternal NOEL:** 25 mg/kg/day (based upon the treatment-related clinical signs and lower food consumption noted for the dams in the 75 mg/kg group); **Developmental NOEL:** 200 mg/kg/day (based upon the lack of treatment-related effects upon the fetuses in the 200 mg/kg group); **Study acceptable.** (Moore, 11/25/13)

53209-0007; 271741; "P4150: Dose Range Finding Study in Rats Preliminary to Teratogenicity Study"; (S.J. Barton; Inveresk Research International, Tranent, EH33 2NE, Scotland; Project No. 490725; 11/16/93); Eight mated Sprague-Dawley female rats/group were dosed orally by gavage with 0 (vehicle: distilled water), 25, 50, 100 or 150 mg/kg/day of P4150 (Lonzabac 12) (batch no. PN-93-12; a.i.: 90%) from day 6 through day 16 of gestation. Another group of 8 unmated females were dosed for 7 days with 200 mg/kg of the test material. Post-dosing salivation was noted for animals in the 50 mg/kg group and above. No treatment-related effect on mean body weight or food consumption was evident for the mated animals. The animals in the 200 mg/kg group demonstrated minimal body weight gain over the course of their treatment. There was no apparent treatment-related effect on fertility or fetal weight. Based on these results, treatment levels of 25, 75 and 200 mg/kg/day were selected for the guideline rat teratology study. **Supplemental Study**. (Moore, 11/13/13)

Rabbit

No study submitted.

NEUROTOXICITY

Acute neurotoxicity, rat

No study submitted.

90-day neurotoxicity, rat

No study submitted.

Developmental neurotoxicity, rat

No study submitted.

Delayed neurotoxicity, hen

No study submitted.

IMMUNOTOXICITY

See Rat Subchronic Repeated Dosing Dermal Toxicity and Immunotoxicity Study above.

ENDOCRINE DISRUPTOR STUDIES

No studies submitted

SUPPLEMENTAL STUDIES

No studies submitted.