Pesticide Fact Sheet

Name of Chemical: **Amisulbrom**

Reason for Issuance: **New Active Ingredient; Tolerances for Imported Commodities**

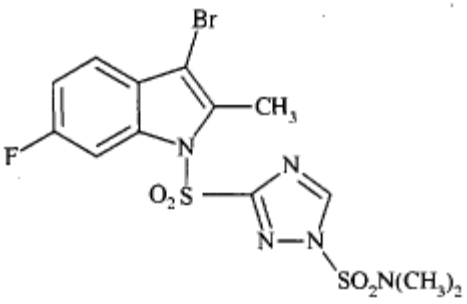
Date Issued: **September 16, 2011**

I. DESCRIPTION OF CHEMICAL

Common Name	Amisulbrom
Company Experimental Name	NC-224
IUPAC Name	3-(3-bromo-6-fluoro-2-methylindol-1-ylsulfonyl)-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-1-sulfonamide
CAS Name	3-[(3-bromo-6-fluoro-2-methyl-1H-indole-1-yl)sulfonyl]-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide
Year of Initial Registration	Not registered in the US
Chemical Abstracts Service (CAS) Number	348635-87-0
EPA Chemical Code	016330
Pesticide Type	Fungicide
Chemical Class	Sulfonamide
Company	Nissan Chemical Industries, Ltd.
Mode of Action:	Oomycete-specific fungicide which acts by inhibiting mitochondrial respiration. The Fungicide Resistance Action

Committee has categorized amisulbrom as a QII (Quinine Insider Inhibitor) based upon this mode of action.

Chemical Structure



II. USE PATTERN AND FORMULATIONS

Amisulbrom is a fungicide active ingredient developed by Nissan Chemical Industries Limited. Amisulbrom is not currently registered in the United States (US); however tolerances have been established for commodities imported into the US. Amisulbrom is registered for use on grape and potatoes grown in several European countries, and a tomato use is currently under review in the European Union. The active ingredient for use on grape and tomato is formulated as a suspension concentrate for foliar applications. .

III. HUMAN HEALTH RISK ASSESSMENT

Acute Toxicity

Technical amisulbrom has low acute toxicity (Toxicity Category IV) via the oral, dermal and inhalation routes of exposure. Amisulbrom is not an eye or dermal irritant, and did not show evidence of sensitization.

Subchronic, Chronic, Other Toxicity

Rat, mouse, and rabbit studies indicate that amisulbrom systemic toxicity is primarily characterized by decreases in body weight and body weight gain, and reduced food consumption and/or efficiency. Neither the rat subchronic neurotoxicity screening studies nor the rat multigenerational reproduction study or other subchronic or chronic studies indicated specific neurotoxicity responses to amisulbrom.

The T-cell dependent antibody response (TDAR) assay showed no evidence of treatment-related effects in rat and mouse immunotoxicity studies. The rat developmental toxicity study demonstrated cleft palate and other malformations only at the highest doses (1,000 mg/kg/day).

There were no effects in the fetuses in the rabbit developmental toxicity study at the highest dose tested. Amisulbrom was not associated with genetic toxicity or mutagenicity concerns.

Carcinogenicity

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), amisulbrom is classified as **"Suggestive Evidence of Carcinogenic Potential."** This classification is based on: liver tumors in male mice at both adequate and excessive doses; liver tumors in both sexes of rats only at an excessive dose; and forestomach tumors in female rats, also only at an excessive dose. In the case of amisulbrom, a cancer risk from dietary exposure is of low concern based on the following considerations:

- The liver tumors seen in male mice only were benign with no progression to malignancy;
- The liver tumors in rats seen only at excessive doses (i.e., greater than the Limit Dose of 1000 mg/kg/day) were also benign with no progression to malignancy;
- The forestomach tumors seen only in female rats occurred only at an excessive dose which was greater than the Limit-Dose;
- None of these tumors resulted in reduced latency ; and
- There is no concern for mutagenicity/genotoxicity.

Given that the only evidence showing any concern for carcinogenicity is the occurrence of benign liver tumors in one sex and one species (i.e., male mice), the Agency has determined that the chronic reference dose will adequately account for all chronic effects, including carcinogenicity, likely to result from exposure to amisulbrom.

Food Quality Protection Act (FQPA) Safety Factor

EPA has determined that reliable data show the safety of infants and children would be adequately protected if the FQPA safety factor were reduced to 1X. The toxicity database is complete for assessing increased susceptibility under FQPA.

Neurotoxicity: Neither the rat subchronic neurotoxicity screening studies nor the rat multigenerational reproduction study or other subchronic or chronic studies indicated specific neurotoxicity responses to amisulbrom. Although the acute neurotoxicity study observed decreased brain weight, this effect occurred only at the very high limit dose for acute neurotoxicity testing, in only one sex, and a "no-observed-adverse- effect- level" (NOAEL) was identified. Therefore, there is no need for a developmental neurotoxicity study or additional uncertainty factors to account for neurotoxicity.

Prenatal Developmental/Reproductive Toxicity: There was an apparent indication of prenatal sensitivity in the rat developmental toxicity study. The NOAEL for the offspring in the rat developmental study was 300 mg/kg/day. There were no indications of increased postnatal offspring sensitivity in the rat reproduction study where the NOAEL (~54 mg/kg/day) and the "lowest-observed-adverse-effect-level" or LOAEL (~274 mg/kg/day) for the pups was the same as for the parents. Since effects in the rat pups in the developmental toxicity study occur at a dose (1000 mg/kg/day) well above the NOAELs used for risk assessment (54 and 200 mg/kg/day), no additional uncertainty factor for sensitivity/susceptibility in the developing animal is needed because the application of the lower NOAEL will be protective against

possible developmental effects in the offspring. Based on the available data and the selection of risk assessment endpoints that are protective of developmental effects, there are no residual uncertainties with regard to pre- and/or postnatal toxicity.

Human Exposure and Risk Assessment

To assess the potential risks to human health from dietary exposures to residues of amisulbrom, the Agency conducted screening-level acute and chronic dietary risk assessments using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (*i.e.*, the dose which the Agency has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional Safety Factor, if retained. An uncertainty factor of 100X was applied for oral exposure routes (10X for interspecies extrapolation, 10X for intraspecies variation). For amisulbrom acute and chronic exposures, the Agency is concerned when estimated dietary risk exceeds 100% of the PAD.

Amisulbrom contains a substituted triazole ring. However, grape, tomato, rat, and goat metabolism studies found only low levels of free triazole and/or triazole related compounds. Consequently, triazole compounds were not included in the residue definition for tolerance enforcement or risk assessment.

Since the active ingredient is not registered for use in the United States, there are no drinking water, occupational, or residential exposures associated with the requested tolerances for imported commodities. Therefore, these exposures were not evaluated in this assessment.

Acute Dietary: The acute PAD (aPAD) was based on the observation of a 7% decrease in brain weight in the rat acute neurotoxicity screen study at a LOAEL of 2000 mg/kg [NOAEL = 200 mg/kg]. This dose and endpoint was protective of a rat developmental toxicity study, which showed indications of developmental effects at 1000 mg/kg/day and a NOAEL of 300 mg/kg/day.

A conservative acute dietary (food only) exposure analysis was performed for the general U.S. population and standard population subgroups. Tolerance level residues and 100 percent crop treated assumptions were used. DEEM default processing factors were used to modify the tolerance values. Acute dietary risk estimates are not of concern for the general population or any other population subgroup. At the 95^{th} percentile, exposures were < 1% aPAD for all population subgroups.

Chronic Dietary: The chronic PAD (cPAD) was selected from five studies: the combined chronic toxicity/carcinogenicity study in rats, the multigeneration reproduction study in rats, the mouse carcinogenicity study, and the subchronic and chronic dog studies. The chronic dietary LOAEL of 96 mg/kg/day was selected from the combined chronic toxicity/carcinogenicity study in rats [decreased body weight, body weight gains in both sexes, and indications of hepatotoxicity and nephrotoxicity]; while the NOAEL of 54 mg/kg/day was selected from the multigeneration study [parental systemic NOAEL].

A conservative chronic dietary (food only) exposure analysis was performed for the general U.S. population and standard population subgroups. Tolerance level residues and 100 percent crop treated assumptions were used. DEEM default processing factors were used to modify the tolerance values. Chronic dietary risk estimates are not of concern for the general population or any other population subgroup. Exposures were < 1% cPAD for all population subgroups.

Cancer: Amisulbrom is classified as "Suggestive Evidence of Carcinogenic Potential." Since the evidence as a whole is not strong enough to warrant a quantitative estimation of human risk, the Agency has determined that the chronic PAD will adequately account for all chronic effects, including carcinogenicity, likely to result from exposure to amisulbrom. As noted, there are no chronic risks of concern.

Aggregate Exposure and Risk

An aggregate assessment is not relevant for uses on imported commodities. There are no pesticide registrations in the US associated with the established tolerances; therefore, the presence of amisulbrom in drinking water in this country resulting from the treatment of crops is not expected.

The dietary food exposure assessments were performed based on 100% crop treated and tolerance-level residues. Since there are no currently registered or proposed uses of amisulbrom in the USA and adequate food residue data are available, these assessments will not underestimate the exposure and risks posed by amisulbrom.

Occupational Exposure and Risk

Since there are no currently registered or proposed uses of amisulbrom in the US, an occupational assessment is not relevant for uses on imported commodities.

IV. ECOLOGICAL RISK ASSESSMENT

Since there are no currently registered or proposed uses of amisulbrom in the US, an ecological risk assessment is not relevant for uses on imported commodities.

V. REGULATORY DECISION

The registrant, Nissan Chemical Industries Limited, submitted applications requesting establishment of tolerances for residues of amisulbrom in or on grape and tomato, including processed commodities imported into the US. Amisulbrom is not currently registered in the United States.

The Agency established tolerances for residues of amisulbrom, including its metabolites and degradates, in or on grape at 0.40 ppm; grape, raisin at 1.0 ppm; tomato at 0.50 ppm; and tomato, paste at 1.2 ppm.

The human health risk assessment concluded that the database is complete and adequate to support the proposed tolerances. Unrefined and conservative estimates of dietary exposures (food only, as there are no drinking water or residential exposures associated with imported commodities) from amisulbrom residues are below the Agency's level of concern. The acute and the chronic dietary risk estimates are not of concern for the general population or any other population subgroup. Exposures were equivalent to < 1% aPAD and < 1% cPAD for all population subgroups. EPA concluded that regulation based on the chronic reference dose will be protective for both chronic and carcinogenic risks. As noted, there are no chronic risks of concern. The Agency concluded that there is a reasonable certainty that no harm will result to the general population or to infants and children from exposure to amisulbrom residues.

Specific information on the studies received, the nature of the adverse effects caused by amisulbrom, and the Agency's human health risk assessment can be found at http://*www.regulations.gov* in document "Amisulbrom**.** Human-Health Risk Assessment for the Establishment of Tolerances for Amisulbrom Fungicide in/on Imported Grape and Tomato" in docket ID number EPA-HQ-OPP-2010-0186.

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APPENDIX I - Summary of Physical and Chemical Properties

Parameter	Value
Melting point	128.6-130.0 ºC
pH	6.1 for a 1% suspension
Density (at 20 ºC)	Relative to water at 4 ºC 1.72 for 99.8% Technical Grade 1.61 for 99.1% Pure Grade
Water solubility	0.11 mg/L in water at 20 ºC
Solvent solubility	g/L at 20 ºC Hexane 0.2643 Toluene 88.63 Dichloromethane >250 Acetone >250 Ethyl acetate >250 Methanol 10.11 Octanol 2.599
Vapor pressure (at 25 ºC, extrapolated)	1.8×10^{-8} Pa
Henry's Law Constant (at 20 ºC)	2.8×10^{-5} Pa m^3 mol^{-1}
Octanol/water partition coefficient, $Log(K_{OW})$	4.4 at 40 °C
UV/visible absorption spectrum	Neutral methanol medium: λ_{max} 254 nm, ε 11300 M^{-1} cm^{-1} Acidic methanol/water medium: λ_{max} 254 nm, ε 11500 M^{-1} cm^{-1}

APPENDIX II - Toxicity Data

Acute Toxicity

Study Type	Results	Toxicity Category
Acute Oral – Rat	LD_{50} > 5000 mg//kg bw	IV
Acute Dermal – Rat	LD_{50} > 5000 mg//kg bw	IV
Acute Inhalation – Rat	LC_{50} > 2.85 mg/l (MAC)	IV
Primary Eye Irritation – Rabbit	Non-irritant	IV
Primary Skin Irritation – Rabbit	Non-irritant	IV
Dermal Sensitization (Guinea Pig Maximization test)	No evidence (M&K)	--

Subchronic, Chronic, Other Toxicity

Guideline/ Study Type	**Results NOAEL and LOAEL**
Subchronic Studies	
870.3100 – Subchronic rat	NOAEL = 2000 ppm (170.6 mkd) in males and 6300 ppm (587.2 mkd) in females. LOAEL = 6300 ppm (525 mkd in males and 587 mkd in females) based on body weight and gain, food consumption and efficiency and urinary pH (for females). Establishes dosing for cancer study.
870.3100 – subchronic -mouse	NOAEL = 800 ppm (118.8/163.4 mkd) LOAEL = 2500 ppm (400.3/505.6 mkd) – Body weight gain, and food consumption. Suggests 8000 ppm is tolerable for definitive cancer study.
870.3150 – preliminary non rodent (dog)	Dietary dosing unpalatable. Converted to capsule and tolerable at 1000 mkd.
870-3150 – Subchronic non rodent (dog)	No NOAEL. LOAEL = 100 mkd (lung fibrosis).
Developmental and Reproduction and Special related studies	
870-3700a – rat developmental – pilot	NOAEL > 1500 mkd (HDT) Note: There were no reported incidents of cleft palate.
870-3700a – rat developmental	<u>Maternal:</u> NOAEL = 1000 mkd (HDT) <u>Developmental:</u> NOAEL = 300 mkd. LOAEL = 1000 mkd based on cleft palate and bent scapula and other (presumably related) alterations.
870-3700b – rabbit developmental	<u>Maternal</u>: NOAEL = 30 mkd. LOAEL = 100 mkd based on body weight and feed consumption decease. <u>Developmental:</u> NOAEL = 300 mkd (HDT)
870-3800 – rat multi generation	<u>Parental Systemic</u>:

Guideline/ Study Type	Results NOAEL and LOAEL
reproduction	NOAEL = 600 ppm (53.8/58.8 mkd). LOAEL = 3000 ppm (274/300 mkd) based on decreased body weights and gain and food consumption in both sexes. An effect on increased relative liver weight (8% in males and 5% in females) is considered threshold in developing offspring. Offspring toxicity (at birth): NOAEL = 600 ppm (53.8/58.8 mkd). LOAEL = 3000 ppm (274/300 mkd) based on decreased body weight and gain and absolute and relative thymus weight in the F1 and F2 pups. Offspring toxicity (developmental): NOAEL = 600 ppm (53.8/58.8 mkd). LOAEL = 3000 ppm (274/300 mkd) based on atrophy of the ovary, decreased uterus weight and delayed vaginal opening. Conditions greater and reproductive failure for the F1 parental groups at 15,000 ppm producing only 2 F2 litters.
Special studies for effects on genitals	Conclusions on studies and classification not being made at this time. Studies may eventually be included in a WOE assessment of a MOA for the effects on amisulbrom on the female reproductive system and the basis for reproductive failure at the high dose in the multigenerational reproduction study.
Chronic dosing and carcinogenicity	
870-4100 -Chronic toxicity non-rodent (dog)	NOAEL = 10 mkd. LOAEL = 100 mkd based on liquid stools
870-4200 – carcinogenicity - mouse	NOAEL = 11.6/13.5 mkd for males/females. LOAEL = 97.8/120.6 mkd based on decreased body weight and gain, increased liver weight and liver masses in males and the cecum was associated dark vasculature and histologically with increased incidence of submucosal venules mural pigmentation and both submucosal and mucosal pigmented cells. Hepatocellular adenomas in males at 800 ppm and above.
870-4300 – combined chronic and carcinogenicity – rat.	NOAEL = 11.1 and 14.3 mkd in males and females. LOAEL = 96 and 129.2 mkd in males and females based on decreased body weights and gains in both sexes, and indications of hepato and nephro toxicity. Liver (pair-wise and trend) and stomach (trend) tumors at 10,000 and 20,000 ppm.
Mutagenicity/Genetic Toxicity	
870.5100 – Ames test	No evidence of mutagenicity.
870.5100-Ames test	No evidence of mutagenicity.
870.5300 – chromosome aberrations in human lymphocytes	No evidence of chromosome aberrations.
870.5300 – Mouse lymphoma assay	No evidence of mutagenicity.
870.5395 – induction of micronuclei in bone marrow treated mice	No evidence of induction of polychromatic erythrocytes in bone marrow.
870.5395 – mouse micronucleus test	No evidence of chromosome damage.
870.5395 – mouse micronucleus test	No evidence of effects.
870.5550. Unscheduled DNA	No evidence of UDS in rat hepatocytes.

Guideline/ Study Type	Results NOAEL and LOAEL
synthesis	
Neurotoxicity	
870-6200 – acute neurotox screen	NOAEL = 200 mk. LOAEL = 2000 mk based on slight decrease (7%) in brain weight in males
870-6200 – subchronic neurotox screen	No evidence of neurotoxicity up to 10,000 ppm (860 to 1132 mkd). NOAEL (systemic) = 300 ppm (23 to 29 mkd). LOAEL = 3000 ppm (246/313 mkd) based on decreased body weight.
870.-6300 – developmental neurotoxicity	Study not required [ToxSac meeting December 1, 2010].
Metabolism and Pharmacokinetics	
870.7485. General metabolism	Absorption, distribution, excretion and metabolites characterized. Most recovered in feces and bile dust excretion predominates. About 50% absorbed at 10 mg and only about 5% absorbed at 1000 mg from the gastrointestinal tract. < 0.5% remains in the carcass (liver and kidney). Metabolites identified but no free triazole.
Immunotoxicity	
870.7800 – immunotox -rat	No immunotoxic effect detected.
870-7800 – immunotox - mouse	No immunotoxic effect detected.

APPENDIX III – Data Base Supporting the Tolerances for Amisulbrom

MRID	Citation
47918000	Nissan Chemical Industries, Ltd. (2009) Submission of Product Chemistry, Toxicity, and Residue Data in Support of the Petition for Tolerance of Amisulbrom. Transmittal of 70 Studies.
47918001	Sato, T. (2009) Product Chemistry of Amisulbrom Technical Product. Project Number: NCI/224/H2106. Unpublished study prepared by Nissan Chemical Company, Ltd. 118 p.
47918002	Takehara, K. (2005) Batch Analysis of NC-224 Technical Product: Final Report. Project Number: NCI/2005/024. Unpublished study prepared by Nissan Chemical Industries, Ltd. 53 p.
47918003	Takehara, K. (2005) Validation of the Method for Determination of the Active Ingredient in NC-224 Technical Product: Final Report. Project Number: NCI/2004/066. Unpublished study prepared by Nissan Chemical Industries, Ltd. 36 p.
47918004	Takehara, K. (2005) Validation of the Method for Determination of Impurities in NC-224 Technical Product: Final Report. Project Number: NCI/2005/020. Unpublished study prepared by Nissan Chemical Industries, Ltd. 60 p.
47918005	McCombie, W. (2009) Amisulbrom Technical Fungicide (NC-2224): Waiver Requests for Chemistry Data. Unpublished study prepared by Lewis & Harrison. 5 p.
47918006	Comb, A. (2005) NC-224 (Technical Grade): Appearance. Project Number: NAS/0782, NAS0782/053827. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 15 p.
47918007	Takehara, K. (2003) NC-224, Melting Point: Final Report. Project Number: NCI/2002/054. Unpublished study prepared by Nissan Chemical Industries, Ltd. 15 p.
47918008	Comb, A. (2003) NC-224 (Pure Grade): Relative Density. Project Number: NAS/446, NAS446/024103. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 17 p.
47918009	Comb, A. (2003) NC-224 (Technical Grade): Relative Density. Project Number: NAS/451, NAS451/024188. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 17 p.
47918010	Takehara, K. (2003) NC-224, Water Solubility: Final Report. Project Number: NCI/2002/041. Unpublished study prepared by Nissan Chemical Industries, Ltd. 32 p.
47918011	Ogi, N. (2003) NC-224 (Technical Grade), Solubility in Organic Solvents: Final Report. Project Number: NCI/2002/074. Unpublished study prepared by Nissan Chemical Industries, Ltd. 32 p.
47918012	Comb, A. (2003) NC-224: Vapour Pressure. Project Number: NAS448/024119, NAS/448. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 23 p.
47918013	Comb, A. (2003) NC-224: pH Determination. Project Number: NAS/457, NAS457/024118. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 15 p.
47918014	Comb, A. (2003) NC-224: Stability. Project Number: NAS455/024415, NAS/455. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 33 p.
47918015	Comb, A. (2003) NC-224: Oxidation/Reduction: Chemical Incompatibility. Project Number: NAS456/024117, NAS/456. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 16 p.
47918016	Comb, A. (2003) NC-224: Flammability (Solids). Project Number: NAS450/024105, NAS/450. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 15 p.
47918017	Comb, A. (2003) NC-224: Explosive Properties. Project Number: NAS453/024107, NAS/453. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 17 p.

47918018	Comb, A. (2005) NC-224 (Technical Grade): Two Year Storage Stability. Project Number: NAS464/043692, NAS/464. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 31 p.
47918019	Matsue, H. (2003) UV/VIS and IR Spectra of NC-224: Final Report. Project Number: 03021. Unpublished study prepared by Hodogaya Contract Laboratory Co., Ltd. 34 p.
47918020	Ogi, N. (2003) NC-224, Nuclear Magnetic Resonance and Mass Spectra: Final Report. Project Number: NCI/2002/069. Unpublished study prepared by Nissan Chemical Industries, Ltd. 22 p.
47918021	Yokouchi, K. (2003) NC-224: Calculation of Volatility (Henry's Law Constant). Project Number: NCI/224/H1501. Unpublished study prepared by Nissan Chemical Industries, Ltd. 7 p.
47918022	McCombie, W. (2009) Product Chemistry of Amisulbrom: End-Use Product. Unpublished study prepared by Lewis & Harrison. 70 p.
47918023	Arrowsmith, W. (2003) NC-224: Acute Oral Toxicity to the Rat: (Acute Toxic Class Method). Project Number: NAS/445/024159/AC, NAS/445. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 16 p.
47918024	Dreher, D. (2005) IT-4: Acute Oral Toxicity Study in the Female Rat (Acute Toxic Class): Final Report. Project Number: 0306/147. Unpublished study prepared by Covance Laboratories, Ltd. 25 p.
47918025	Blee, M. (2003) NC-224: Toxicity Study by Dietary Administration to Han Wistar Rats for 13 Weeks. Project Number: NAS/369, NAS/369/022366. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 328 p.
47918026	Blee, M. (2003) NC-224: Preliminary Toxicity Study by Dietary Administration to CD-1 Mice for 13 Weeks: Final Report. Project Number: NAS/370, NAS/370/022365. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 224 p.
47918027	Kilpatrick, H. (2003) NC-224: Toxicity Study by Oral Capsule Administration to Beagle Dogs for 13 Weeks. Project Number: NAS/391, NAS/391/023346. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 217 p.
47918028	Barker, M. (2001) A-992176: Pilot Toxicity Study by Dietary/Capsule Administration to Male Beagle Dogs for 13 Weeks. Project Number: NAS/330/012630. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 102 p.
47918029	Cooper, S. (2004) NC-224: Toxicity Study By Dermal Administration to CD Rats for 21 Days. Project Number: NAS/567, NAS/567/042107. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 256 p.
47918030	Fulcher, S. (2004) NC-224: Study of Effects on Embryo-Fetal Development in Han Wistar Rats Treated by Oral Gavage Administration. Project Number: NAS/434, NAS/434/032161. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 135 p.
47918031	Fulcher, S. (2004) NC-224: Study Effects on Embryo-Fetal Toxicity in the Rabbit by Oral Gavage Administration. Project Number: NAS/435, NAS/435/032162. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 113 p.
47918032	Fulcher, S. (2005) NC-224: Study of Reproductive Performance in Han Wistar Rats Treated Continuously Through Two Successive Generations by Dietary Administration. Project Number: NAS/525/033720, NAS/525. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 1111 p.
47918033	Kilpatrick, H. (2005) NC-224: Toxicity Study by Oral Capsule Administration to Beagle Dogs for 52 Weeks: Amended Final Report. Project Number: NAS/429, NAS/429/042014. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 327 p.
47918034	Blee, M. (2005) NC-224: Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks. Project Number: NAS/428, NAS/428/033139. Unpublished study prepared by Huntingdon

	Life Sciences, Ltd. 1365 p.
47918035	Blee, M. (2005) NC-224: Combined Carcinogenicity and Toxicity Study by Dietary Administration to Han Wistar Rats for 104 Weeks. Project Number: NAS/427, NAS/427/032648. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 1821 p.
47918036	May, K. (2002) NC-224: Bacterial Reverse Mutation Test: (Salmonella typhimurium, Escherichia coli). Project Number: NAS/440, NAS/440/023917. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 31 p.
47918037	Johnson, M. (2005) IT-4: Reverse Mutation in Four Histidine-Requiring Stains of Salmonella typhimurium and One Tryptophan-Requiring Strain of Escherichia coli: Final Report. Project Number: 306/145, 306/145/D6171. Unpublished study prepared by Covance Laboratories, Ltd. 58 p.
47918038	Lloyd, M. (2004) NC-224: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) Using the Microtitre Fluctuation Technique: Final Report. Project Number: 306/131, 306/131/D6173. Unpublished study prepared by Covance Laboratories, Ltd. 55 p.
47918039	Kumaravel, T. (2004) NC-224: Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes: Final Report. Project Number: 306/130, 306/130/D6172. Unpublished study prepared by Covance Laboratories, Ltd. 52 p.
47918040	Whitwell, J. (2005) IT-4: Induction of Micronuclei in the Bone Marrow of Treated Mice: Final Report. Project Number: 306/146, 306/146/D6172. Unpublished study prepared by Covance Laboratories, Ltd. 34 p.
47918041	Mehmood, Z. (2003) NC-224: Mouse Micronucleus Test. Project Number: NAS/458, NAS/458/024353. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 28 p.
47918042	Hynes, G. (2007) NC-224: Mouse Micronucleus Test. Project Number: NAS/0951, NAS/0951/074029. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 32 p.
47918043	Saitou, Y. (2005) In Vivo/ In Vitro Unsheduled DNA Synthesis (UDS) Test on NC-224 Using Rat Livers: Final Report. Project Number: B041599. Unpublished study prepared by Mitsubishi Chemical Safety Institute, Ltd. 55 p.
47918044	Chapman, M. (2006) NC-224: Neurotoxicity Study by a Single Oral Administration to CD Rats Followed by a 14-Day Observation Period. Project Number: NAS/716, NAS/716/053236. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 334 p.
47918045	Chapman, M. (2007) NC-224: Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks. Project Number: NAS/0795, NAS/0795/063654. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 375 p.
47918046	Langford-Polland, A. (2004) NC-224: Metabolism in Rats: Single Oral Administration. Project Number: NAS/439, NAS/439/033728. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 400 p.
47918047	Itoh, K. (2005) General Pharmacology Study of NC-224 (in Rats and Dogs): Final Report. Project Number: 8640/080/079. Unpublished study prepared by Biosafety Research Center, Foods, Drugs and Pesticides. 58 p.
47918048	Brown, L. (2009) NC-224: 4-Week Dietary Immunotoxicity Study in the Rat. Project Number: ONE0011. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 182 p.
47918049	Moore, E. (2009) NC-224: 4-Week Dietary Immunotoxicity Study in the Mouse. Project Number: ONE0010. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 206 p.
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