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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

March 1, 2005

MEMORANDUM

SUBJECT: NITRAPYRIN. Revised HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code: 069203, DP Barcode D298455

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The attached revised Human Health Assessment for the nitrapyrin RED document was generated as part of Phase 1 of the Interim Public Participation Process. *This is a revision of the original Risk Assessment for nitrapyrin, (S. Tadayon September 30, 2004). This document has been revised to address comments made by the registrants during public comment period.* The Office of Pesticide Programs (OPP) Health Effects Division's (HED) chapter reflects the Agency's current policies and guidelines concerning the risk assessment. This chapter includes a summary of the product chemistry and residue chemistry dietary assessment from David Soderberg, toxicology review from John Doherty, occupational exposure from Seyed Tadayon, drinking water exposures from

Amer Almudallal [Environmental Fate and Effects Division (EFED)], as well as risk assessment and characterization from Seyed Tadayon.

The disciplinary science chapters and other supporting documents are included as appendices as follows:

Nitrapyrin - Report of the Hazard Identification Assessment Review Committee (TXR No. 0052387, J. Doherty, 3/1/04).

Nitrapyrin - Toxicology Chapter for the HED Risk Assessment (TXR No. 0050421, J. Doherty, 3/13/04) .

Nitrapyrin - HED Chemistry Chapter of the RED: Summary of Product and Residue Chemistry Residue Data (David Soderberg , 04/2004).

Nitrapyrin - Acute (Probabilistic) and Chronic Dietary Exposure Assessments.

Nitrapyrin - The Occupational and Residential Exposure Assessments (S Tadayon 3/2004).

Nitrapyrin - Product Chemistry Considerations (David Soderberg , 02/2004).

Tier1Estimated Environmental Concentrations of nitrapyrin for use in the Human Health Risk Assessment (D299121, Amer Al-mudallal 4/14/2004).

Nitrapyrin -Conclusions of the team review of metabolism information (D299923, David Soderberg , 02/23/2004).

Table of Content

1.0 EXECUTIVE SUMMARY

The Agency has conducted a human health risk assessment for the active ingredient nitrapyrin, [2-chloro-6-(trichloromethyl) pyridine], for the purpose of making a reregistration eligibility decision. Because of the selective activity to azotobacter, nitrapyrin can be used as an nitrogen nitration inhibitor and soil bactericide, and can delay the nitration of ammonium ion in soil when used together with urea and nitrogen fertilizer. Nitrapyrin, the active ingredient in Stay-N-2000® and N-Serve-24E®, inhibits (temporarily slows, but does not stop) the nitrification process at the conversion of ammonium to nitrite. By slowing nitrification, nitrapyrin slows the formation of nitrate. If more ammonium remains in the soil during a wet period then less nitrate is present and subject to loss. It is degraded predominantly in soil by chemical hydrolysis, which lessens effectiveness over time. Degradation is temperature dependent, so warm soils that speed nitrification also speed nitrapyrin breakdown, which means effectiveness is lower, nitrification reestablishes more quickly, and longevity is shorter. The Registrant, Dow Agro Science is supporting use of nitrapyrin on corn, sorghum and wheat. Nitrapyrin is the only microbiocide available to control nitrosomonas bacteria. Nitrate nitrogen is the only form of nitrogen which is of major importance in nitrogen loss from most soils. Once nitrogen is converted to nitrate, it would be difficult to reduce losses except improving the drainage of the soil.

Nitrapyrin is applied via soil injection equipment with anhydrous ammonia fertilizer. This microbiocide can be applied once per season and at an application rate of 0.5 to 1.0 pounds ai/acre. Nitrapyrin is applied directly to the soil, rather than the crops. Registered use sites include corn, sorghum and wheat. The only formulation marketed is an emulsifiable concentrate.

Hazard Assessment

Nitrapyrin is classified as Toxicity III for acute oral (LD_{50} 1.07 gm/kg for males and 1.23 gm/kg for females), dermal (LD_{50}> 2000 mg/kg) and inhalation (LC_{50} > 0.03 mg/L Not Classifiable). Nitrapyrin is not considered a dermal irritant (Toxicity Category IV) but does have some properties as an ocular irritant (Toxicity Category II). Nitrapyrin was demonstrated to be positive in a modified Maguire dermal sensitization study.

In both subchronic and chronic studies, the major target organ of nitrapyrin is the liver. Effects were consistent among the species tested (rat, dog, mouse) in both subchronic and chronic studies and typically included enlarged livers. In dogs liver toxicity was indicated by changes in cholesterol, alkaline phosphatase, liver weight and hypertrophy. In rats, liver weight was increased and this was associated with clinical chemistry changes such as increases in albumin, alanine aminotransferase, cholesterol, hepatocellular hypertrophy and centrilobular vacuolization consistent with fatty change. In mice, the liver weight changes were associated with several histopathological findings ranging from centrilobular and panlobular hepatocyte hypertrophy, mitotic figures and eventual necrosis to and including bile duct proliferation.

Food Quality Protection Act (FQPA) Decision : On March 1, 2004, The HED Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for nitrapyrin with regard to the acute and chronic Reference Doses (RfDs) and toxicological endpoint selection for use as appropriate in occupational /residential exposure assessments. The potential for increased susceptibility of infants and children from exposure to nitrapyrin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC concluded that the toxicology database for nitrapyrin is complete. The HIARC further concluded that there is not a concern for neurotoxicity or for pre- and /or postnatal toxicity resulting from exposure to nitrapyrin. The HIARC concluded there are no concerns or residual uncertainties for pre- and or postnatal toxicity. On this basis, the HIARC concluded that the special FQPA safety factor should be removed (i.e., reduced to1X) for all potential exposure scenarios to nitrapyrin. The recommendation is based on the following:

*Neither the rat or rabbit developmental toxicity studies nor the rat two-generation reproduction toxicity study demonstrated increased susceptibility of the fetuses or offspring.
*There are no concerns or residual uncertainties for pre and/or post-natal toxicity.
*There are no proposed residential uses.
*The dietary and drinking water risk assessments use conservative assumptions to estimate exposure and do not underestimate risks.

Dose Response Assessment: On March 1, 2004, the Health Effects Division (HED Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for nitrapyrin with regard to the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The HIARC report indicated that there are toxicological endpoints of concern for nitrapyrin. The recommendation are as follows:

*For general population, including infants and children, the dose and endpoint for establishing a chronic dietary reference dose (cRfD) is a NOAEL of 3 mg/kg/day from the chronic dog study with a LOAEL of 15 mg/kg/day based on liver effects. An uncertainty factor of 100 was selected (10x inter-species extrapolation and 10x intra-species variability), Therefore, the theoretical chronic RfD or the theoretical Chronic Population Adjusted Dose(cPAD) would be 0.03 mg/kg/day.

*An acute dietary RfD was not established because an appropriate endpoint attributable to a single dose was not available from any study including the developmental toxicity studies. The crooked hyoid seen in the fetuses of rabbits was not considered to be the result of a single exposure (dose) and therefore was not selected for risk assessment.

*Dermal absorption value of 46% was bases on a rat dermal absorption study, to represent the residual chemical that could be absorbed. An absorption factor of 100% was applied for inhalation exposures.

Short- and intermediate-term occupational dermal and inhalation endpoints of concern were identified. Long-term occupational inhalation and dermal endpoints were not identified since there

are no long-term activities associated with nitrapyrin. Due to lack of inhalation studies, the HIARC selected an endpoint from oral studies for inhalation and dermal risk assessments.

*The occupational short-term (1-30days) dermal and inhalation endpoint , NOAEL 10 mg/kg/day, is from developmental oral study in rabbits and is based on common decreases in body weight gain and increased liver weight at a LOAEL of 30 mg/kg/day. The intermediate-term (1-6 months dermal and inhalation endpoints of concern NOAEL (3 mg/kg/day) is from a chronic dog study and is based on liver enzymes, liver weights and liver lesions at a LOAEL of 15 mg/kg/day.

*The short -term incidental oral endpoint, is from a developmental oral study in rabbits and is based on common decreases in body weight gain and increased liver weight at a LOAEL of 30 mg/kg/day. The maternal NOAEL is 10 mg/kg/day. The intermediate-term incidental oral endpoint of concern NOAEL, (3 mg/kg/day) is from a chronic dog study and is based on liver enzymes, liver weights and liver lesions at a LOAEL of 15 mg/kg/day. Because there are no residential uses, endpoints selected for incidental oral exposure were not used in this assessment.

The target MOE of 100 for occupational exposure scenarios was selected based upon 10x for intraspecies variation and 10x for interspecies extrapolation. Because the effects from dermal and inhalation exposure are the same, the doses for these routes and duration were combined.

Nitrapyrin is classified as "likely to be a human carcinogen" based on the mouse study which demonstrated liver, stomach, epididymal and Harderian gland tumors. The Q1* was determined to be 4.25×10^{-2} human equivalents. This classification was reaffirmed on February 9, 2005 following a revisit to the CARC where all of the issues raised by the DOW Company in their SAG review were considered. However, the CARC agreed that the Harderian gland tumors were no longer considered a response to treatment and the forestomach tumors not relevant to human health risk assessment. However, the CARC retained its concern for the epididymal tumors and did not accept the SAG proposed mechanism for liver tumors.

Exposure Assessment

Dietary Exposure Estimates from Food Sources: An acute dietary RfD was not established because an appropriate endpoint attributable to a single dose was not available from any study including the developmental toxicity studies therefore no acute dietary assessment was performed.

Residues of concern for chronic risk assessment and for tolerance assessment for treated crops and rotated crops are parent nitrapyrin and free and conjugated forms of its 6-chloropicolinic acid (6-CPA) metabolite. A refined chronic dietary exposure assessment for nitrapyrin and 6-CPA was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 1.33) and the Lifeline™ Model Version 2.0. The results of the Lifeline™ analysis are consistent with the DEEM-FCID™ results. The exposure assessment used average residues from field trial data for all commodities (corn, sorghum, wheat) except for some processed wheat fractions, for which tolerance level residues were used. Percent crop treated values were incorporated as were processing factors.

Live stock and poultry commodities, including milk and eggs, were not included in this assessment as HED has concluded that, there is no reasonable expectation of finite residues in these commodities.

For all commodities, the results of both the DEEM-FCID™ and Lifeline™ analyses for dietary exposure (food only) yielded exposure results <1% cPAD for the US Population and for all population subgroups, which is below HED level of concern. Dietary exposure results <100% of the cPAD are below HED's level of concern.

A cancer dietary risk assessment was not conducted because the cancer endpoint is relevant only to nitrapyrin, per se, and not to 6-CPA; exposure to nitrapyrin, per se, in the diet is negligible (zero).

Dietary Exposure Estimates from Drinking Water Sources: Monitoring data for nitrapyrin residues in surface and ground water were not available. Consequently, potential human exposure to parent nitrapyrin and it's major degradate 6-chloropicolinic acid (6-CPA) from ingestion of drinking water was assessed by modeling. EFED conducted surface and ground water modeling for nitrapyrin and 6-CPA, separately because a combined residue approach was not possible. The modeling assessments assumed that nitrapyrin and 6-CPA were applied at maximum labeled application rates. 6-CPA was not detected or adequately quantified in all environmental fate studies that are used in the PRZM/EXAMS input parameters. Therefore, no combined residue half-lives (nitrapyrin + 6-CPA) could be determined. This approach to modeling provided separate sets of estimated environmental concentrations (EECs) for nitrapyrin and 6-CPA, respectively, in surface and ground water. Because 6-CPA is the major soil and water degradate of nitrapyrin, and is more mobile than nitrapyrin, EECs for 6-CPA were greater than EECs for nitrapyrin (see Table 8).

Due to the lack of environmental fate data on 6-CPA (with the exception of the adsorption/desorption study), EFED assumed 6-CPA to be stable to all routes of degradation in soil and water. This assumption is expected to result in conservative estimates of the concentration of 6-CPA in water.

The use of nitrapyrin on corn, sorghum, and wheat was modeled using index reservoir scenarios with percent crop area (PCA) adjustment factors. The Texas sorghum scenario produced the highest estimated 1-day (peak) concentration of nitrapyrin in surface water among the modeled scenarios. The estimated concentration of nitrapyrin in surface water in a Texas sorghum IR scenario adjusted for a PCA factor of 0.87 is not expected to exceed 1.21 ppb for the 1 in 10 year annual peak concentration, 0.03 ppb for the 1 in 10 year annual daily mean concentration, and 0.01 ppb for the 30 year annual average concentration. SCI-GROW estimated the concentration of nitrapyrin in shallow ground water sources to be 0.07 ppb. The Oregon wheat scenario produced the highest estimated 1-day (peak) concentration of 6-CPA in water among the modeled scenarios. The estimated concentration of 6-CPA in surface water in an Oregon wheat scenario adjusted for a PCA factor of 0.87 is not expected to exceed 1.71 ppb for the 1 in 10 year annual peak concentration, 1.63 ppb for the 1 in 10 year annual daily mean concentration, and 1.02 ppb for the 30 year annual average

concentration. The estimated concentration of 6-CPA in shallow ground water sources ranged from 30.87 ppb - 278.82 ppb.

For drinking water risk assessment, HED estimated chronic exposures using 1.6 ug/L of 6-CPA in surface water and 31-280 ug/L 6-CPA in groundwater. HED estimated cancer risks from drinking water exposures to nitrapyrin at 0.01 ug/L in surface water and 0.07 ug/L of nitrapyrin in ground water. HED used 6-CPA residues in drinking water to estimate chronic risk because the chronic effects have been determined to be relevant to both nitrapyrin and 6-CPA, and as the major soil and water degradate of nitrapyrin residues of 6-CPA represent the worst-case exposure scenario. HED used residues of nitrapyrin to estimate cancer risk, because the tumors seen in lab animals from toxicity testing have been determined to be relevant to exposure to nitrapyrin, per se, and not 6-CPA.

Residential Exposure Estimates: Products containing nitrapyrin are not intended for residential uses as there are currently no registered home owner uses. Therefore, a residential risk assessment was not conducted.

Occupational Exposure Estimates: Health Effects Division (HED) has determined that there are potential exposures to occupational mixers, loaders, applicators, or other occupational handlers during standard uses associated with nitrapyrin. Two major exposure scenarios were identified for occupational handlers. These scenarios include mixing, loading and applying liquids and sprays via ground booms. The exposure scenarios durations are of short-term (1-30 days) and intermediate-term (1 to 6 months); use patterns do not indicate any long-term use. A total MOE was also calculated because the same endpoint was selected for dermal and inhalation risk assessment.

Calculation of non-cancer occupational risk based on combined dermal and inhalation exposure indicates that all potential exposure scenarios provide a total MOEs ≥ 100 at baseline or with Personal Protective Equipment (PPE). Dermal exposure, rather than inhalation exposure, appears to be the main contributor to the total MOEs for all scenarios. Total exposure estimates do not exceed HED's level of concern.

Cancer risks for occupational dermal and inhalation exposures range from 6.66×10^{-3} to 3.6×10^{-6} at the baseline (long pants, long sleeved shirts and no gloves), 5.58×10^{-5} to 3.6×10^{-6} PPE1(long pants, long sleeved shirts and gloves), 4.4×10^{-5} to 2.90×10^{-6} at PPE2 (long pants, long sleeved shirts, double layer and gloves and no respirator), 3.96×10^{-5} to 2.6×10^{-6} at PPE3 (long pants, long sleeved shirts, double layer, gloves and organic vapor respirator), and 2.02×10^{-5} to 1.20×10^{-6} at engineering control. Overall, these data suggest that none of the evaluated scenarios have cancer risks that exceed 1.00×10^{-4} (the Agency's level of concern for occupational cancer risk begins at $\leq 1.00 \times 10^{-4}$ with all attempts to mitigate risks to $\leq 1.00 \times 10^{-6}$, when possible).

Postapplication contact of workers with nitrapyrin is generally minimal because of the use sites and the mechanization (i.e., automated planting or harvesting) utilized in cultivating these crops. HED believes that there is negligible possibility of exposure and risk from uses of nitrapyrin that are

applied to the soil or soil "directed" pesticides. This presumes workers will have no direct contact with residues in treated soil. In lieu of estimation of a specific REI, HED recommends that the default WPS REI, based on the acute toxicity of the active ingredient, be used for these scenarios. This will provide some measure of protection to workers who reenter treated areas for non-routine activities which may result in contact with treated surfaces. The acute toxicity classification for primary eye irritation of nitrapyrin is category II which requires a 24-hour Restricted Entry Interval (REI).

Aggregate Exposure Scenarios and Risk Conclusions

Aggregate exposure risk assessments were performed for the following scenarios: chronic aggregate exposure based on nitrapyrin and 6-CPA residues in food and 6-CPA residues in drinking water. An acute aggregate assessment was not performed because no acute endpoint was selected. The cancer aggregate assessment is based on residues of nitrapyrin in drinking water only, because residues of nitrapyrin in foods is considered negligible (zero).

Chronic Aggregate Exposure and Risk: The Estimated Environmental Concentrations EECs (highest value) generated by EFED are less than HED's calculated chronic Drinking Water Levels of Comparison DWLOCs for 6-CPA and nitrapyrin in drinking water. The DWLOCs range from 300 µg/L for the population subgroup with the highest food exposure (Children 1 to 2 years old) to 1050 µg/L for the subgroups U.S. Population, Adults 20 to 49 years old, and Adults 50+ years old. HED thus concludes with reasonable certainty that residues of nitrapyrin in drinking water will not contribute significantly to the aggregate chronic human health risk, and that the chronic aggregate exposure from nitrapyrin residues in food and drinking water will not exceed the Agency's level of concern (100% of the chronic PAD) by *any* population subgroup.

Cancer Aggregate Exposure and Risk: An aggregate cancer risk assessment for the U.S. Population based on nitrapyrin was conducted in which food exposure was assumed to be negligible but water exposures were not. The EECs used for the cancer aggregate risk assessment are 0.01 ug/L of nitrapyrin (surface water) and 0.07 ug/L of nitrapyrin (groundwater). The calculated cancer DWLOC is 0.84 ug/L. Since the model-based estimates for allowable concentrations of nitrapyrin in surface water and ground water are below the calculated cancer DWLOC, HED concludes that aggregate exposure to nitrapyrin in food and drinking water will not result in a cancer risk of concern.

Incidents: Relatively few incidents of illness have been reported due to nitrapyrin. Some of the reports suggest that nitrapyrin can be an eye and skin irritant (J Blondell April, 2004) .

Risk Summary: The potential risks from occupational exposure to nitrapyrin are generally below HED's level of concern. There are no postapplication occupational exposures associated with transplanting and/or harvesting crops manually or mechanically that are of concern. The adult male and female populations as a whole had chronic and cancer Drinking Water Levels of Comparison (DWLOC) values that exceed the surface and ground water EECs; consequently, the Agency concludes with reasonable certainty that there is no drinking water risk of concern for these

populations exposure to nitrapyrin or 6 CPA. Chronic DWLOC values derived for infants and children also exceeded the Estimated Environmental Concentrations (EECs) for ground water and surface water are also of no concern to the Agency. The results of both the DEEM-FCID™ and Lifeline™ analyses for dietary exposure (food only) yielded exposure results <1% cPAD for the US Population and for all population subgroups. Dietary exposure results <100% of the cPAD are below HED's level of concern.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Nitrapyrin[2-chloro-6- (trichloromethyl)] pyridine is an ammonical nitrogen stabilizer which inhibits the nitrification of ammonical and urea nitrogen fertilizer in the soil. A single manufacturing use product (MP) registered under the PC Code 069203 was identified as Dow Agro Sciences technical product, EPA Reg. No. 464-434. Only the Dow Agro Sciences 90% technical is subject to a reregistration eligibility decision. (Soderberg, March 2004). The nomenclature and physicochemical Properties of nitrapyrin are presented in tables 1 and 2.

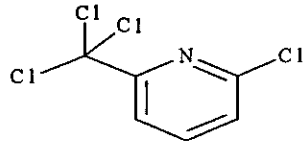
Table 1. Nitrapyrin Nomenclature	
Chemical structure	
Common name	Nitrapyrin
Molecular Formula	$C_6H_3Cl_4N$
Molecular Weight	230.9
IUPAC name	2-chloro-6-trichloromethylpyridine
CAS name	2-chloro-6-(trichloromethyl)pyridine
CAS #	1929-82-4
PC Code	069203

Table 2. Physicochemical Properties of Nitrapyrin		
Parameter	**Value**	**Reference**
Melting point/range	62-63 C	CB No. 6650, 6/19/90, G. Makhijani
pH	not applicable due to very low water solubility	CB No. 6650, 6/19/90, G. Makhijani
Density or specific gravity (20 °C)	1.55 g/mL	Nitrapyrin Update dated 6/11/91
Water solubility (25°C)	92 ppm	Nitrapyrin Update dated 6/11/91
Solvent solubility (20-22°C)	30 g/100 g in ethanol 104 g/100 g in xylene 185 g/100 g in methylene chloride 198 g/100 g in acetone	Nitrapyrin Update dated 6/11/91
Vapor pressure (23°C)	2.8×10^{-5} mm Hg	Nitrapyrin Update dated 6/11/91
Dissociation constant (pK_a)	does not dissociate	Nitrapyrin Update dated 6/11/91
Octanol/water partition coefficient (K_{ow}; 20 C)	520	Nitrapyrin Update dated 6/11/91
UV/vis absorption spectrum	not available	

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Nitrapyrin [(2-chloro-6-(trichloromethyl)pyridine] is a nitrification inhibitor that is used to prolong nitrification of ammonium ions when applied with ammoniacal fertilizers (urea, anhydrous ammonia, etc) and liquid animal wastes. It is used on fields to be planted with corn, wheat and sorghum. It acts by inhibiting *Nitrosomonas* bacteria.

Nitrapyrin is classified as Toxicity III for acute oral (LD_{50} 1.07 gm/kg for males and 1.23 gm/kg for females), dermal (LD_{50}> 2000 mg/kg) and inhalation (LC_{50} > 0.03 mg/L Cannot Classify). Nitrapyrin is not considered a dermal irritant (Toxicity Category IV) but does have some properties as an ocular irritant (Toxicity Category II). Nitrapyrin was demonstrated to be positive in a modified Maguire dermal sensitization study.

Table 3. Acute Toxicity Data on Nitrapyrin

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral - rat	00037519 (1972)	LD_{50} = 1.07 gm/kg ♂ 1.23 gm/kg ♀	III
81-2	Acute Dermal - rabbit	(1986)	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	00158901 (1986)	LC_{50} > 0.03 m/L no effects (technically limited atmospheric conc.)	Can Not Classify*
81-4	Primary Eye Irritation	00158902 (1986)	Corneal opacity to day 14 (2/6), conjunctivitis today 21, iritis to day 7.	II
81-5	Primary Skin Irritation	00037519 (1972)	Very slight erythema and slight exfoliation.	IV
81-6	Dermal Sensitization	00158903 (1986)	Positive in the modified Maguire method.	

* The waxy physical nature of technical nitrapyrin precludes generating aerosols of appropriate atmospheric concentration to meaningfully assess inhalation toxicity

Acute: An acute dietary RfD was not established because an appropriate endpoint attributable to a single dose was not available from any study including the developmental toxicity studies. The crooked hyoid seen in the fetuses of rabbits was not considered to be the result of a single exposure (dose). This observation is considered a variation and not a malformation and is due to the differential development between muscle and bone (ossification) in the fetus and would not be

observed in the newborn (ossification and muscle development complete). Therefore this endpoint was not selected for risk assessment.

Subchronic and Chronic Toxicity: In addition to body weight decreases, the liver was demonstrated to be the principle target organ in rat, mouse and dog subchronic and chronic studies. In dogs liver toxicity was indicated by changes in cholesterol and alkaline phosphatase and liver weight. and hypertrophy. In rats, liver weight was increased and this was associated with clinical chemistry changes such as increases in albumin, alanine aminotransferase and cholesterol and hepatocellular hypertrophy and centrilobular vacuolization consistent with fatty change. In mice, the liver weight changes were associated with several histopathological findings ranging from centrilobular and panlobular hepatocyte hypertrophy, mitotic figures and eventual necrosis and including bile duct proliferation. The stomach was also demonstrated to be a target organ as indicated by hyperkeratosis and/or hyperplasia Epithelial cell vacuolation and/or hyperplasia/hypertrophy was also seen in the duodenum and jejunum. Increased extramedullary hematopoiesis in the spleen was also seen in high dose group mice.

In addition to the liver, the kidney was also demonstrated to be a target organ in male rats only and the weight of evidence indicated that nitrapyrin affects the kidney in a manner consistent with the alpha 2μ globulin model. Consistent with this model, kidney non-neoplastic pathology was evident and there were increases in kidney tumors in male rats. Induction of kidney pathological changes in the alpha 2μ globulin model is not related to human risk assessment.

Reproductive and Developmental toxicity: Nitrapyrin did not demonstrate increased sensitivity to fetuses and offspring. Maternal toxicity consisted of decreases in body weight and liver effects and kidney effects in the rat reproduction study. There were no indications of impaired reproductive performance. Fetal and offspring toxicity was slight and included increased incidence of crooked hyoid in rabbits, ossification decreases in rats and body weight decreases and evidence of hepatic centrilobular hypertrophy with fatty changes in rats in the reproduction study.

Mutagenicity: The mutagenicity data base for nitrapyrin satisfies the current recommendations for testing. However, there is one study conducted by the National Toxicology Program (NTP), that reports that nitrapyrin is mutagenic in the *Salmonella typhimurium* strains TA97, TA98 and TA100 in the presence of S9 metabolic activation. The results of the NTP study are in contrast with the submitted study which did not demonstrate positive mutagenicity effects in these strains. In addition, certain structural activity factors would predict that nitrapyrin could have mutagenic potential.

Neurotoxicity, Endocrine Disruption and Immunotoxicity: Neither the subchronic, chronic, developmental or reproductive rat, mouse, dog or rabbit studies indicated that nitrapyrin was associated with either a specific or an indirect neurotoxic or immunotoxic response or endocrine disruption.

Metabolism: Absorption and elimination of labeled nitrapyrin was rapid and essentially complete by 72 hours. Most (79.56% to 85.48%) of the radioactivity was recovered in the urine with a smaller

amount (11.04% to 13.63%) in the feces. Very little (0.51% to 0.95%) remained in the tissue. There was no unchanged nitrapyrin in the urine and 6-chloropicolinic acid and its glycine conjugate were identified as the metabolites. The glycine conjugate was more common in females and for both sexes following multiple dosing.

Dermal Absorption: Nitrapyrin is readily absorbed by the skin. In a rat dermal absorption study, up to ≈46% of the applied dose of technical nitrapyrin was absorbed after 24 hours of exposure, this includes 34.6% absorbed and 11.4% which could be potentially absorbed.

Carcinogenicity: Nitrapyrin is classified as "likely to be a human carcinogen" based on the mouse study which demonstrated liver, stomach, epididymal and Harderian gland tumors. The Q1* was determined to be 4.25×10^{-2} human equivalents. This classification was reaffirmed on February 9, 2005 following a revisit to the CARC where all of the issues raised by the DOW Company in their SAG review were considered. However, the CARC agreed that the Harderian gland tumors were no longer considered a response to treatment and the forestomach tumors not relevant to human health risk assessment. However, the CARC retained its concern for the epididymal tumors and did not accept the SAG proposed mechanism for liver tumors.

Subchronic, chronic and other types of toxicity studies are summarized in Table 4.

There are no data gaps for nitrapyrin at this time. The HIARC recommended that a 28 day inhalation toxicity study be conducted with nitrapyrin to provide a better endpoint for inhalation risk assessment. However, the waxy physical nature of technical nitrapyrin precludes generating aerosols of appropriate atmospheric concentrations to meaningfully assess the inhalation toxicity. Therefore HED recommends the study requirement be waived. Please refer to the memo dated December 8, 1991 from Linnea Hansen (TXR # 009040) addressing the problems associated with assessing nitrapyrin in inhalation studies.

3.2 FQPA Considerations

On March 1, 2004, The HED Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for nitrapyrin with regard to the acute an chronic Reference Doses (RfDs) and toxicological endpoint selection for use as appropriate in occupational /residential exposure assessments. The potential for increased susceptibility of infants and children from exposure to nitrapyrin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC concluded that the toxicology database for nitrapyrin is complete. The HIARC further concluded that there is not a concern for neurotoxicity or for pre- and /or postnatal toxicity resulting from exposure to nitrapyrin. The HIARC concluded there are no concerns or residual uncertainties for pre- and or postnatal toxicity. On this basis, the HIARC concluded that the special FQPA safety factor should be removed (i.e., reduced to 1X) for all potential exposure scenarios to nitrapyrin.

Table 4. Subchronic, Chronic and Other Toxicity Tables		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rats	Refer to 870.4300 rat chronic feeding/carcinogenicity study below	
870.3100 90-Day feeding - mouse. Pharmaco LSR, Study No.: 93-2278, May 25, 1995	44231802 (1995)* 0, 200, 300 (♂ only), 400, 600 or 800 (♀ only) mg/kg/day. Acceptable/Guideline	NOAEL = 200 mg/kg/day LOAEL = 300 mg/kg/day in males and 400 mg/kg/day in females based on increased liver weight hepatocelluar hypertrophy and enzyme changes.
870.3150 90-Day oral toxicity in nonrodents	Refer to 870.4100 dog chronic study below.	
870.3200 21/28-Day dermal - rabbit Health and Environmental Sciences, Study No.: K-031304-031, Feb. 13, 1992.	42239301 (1992) 0, 100, 500 or 1000 mg/kg/day. Acceptable/Non-Guideline.	NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on liver weight effects.
870.3250 90-Day dermal toxicity	No study available and not required at this time.	
870.3465 90-Day inhalation toxicity	No study available and not required at this time.	
870.3700a Prenatal develop-mental - rats. Pharmaco LSR, Study No.: 93-4050, April 14, 1994.	43210302 (1994, main study) and 43210301 (pilot study). 0, 15, 50 or 120 mg/kg/day (main study). Acceptable/Guideline	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 120 mg/kg/day based on reduced body weight/weight gain and reduced food consumption. **Developmental** NOAEL = 50 mg/kg/day (threshold). LOAEL = 120 mg/kg/day based on possible increase incidence of skeletal variations and delayed ossification and on marginally decreased fetal body weight in female pups only.
870.3700b Prenatal develop-mental - rabbits Dow Laboratory, Study No.: HET 031304-012, October 23, 1985	00153543 (1985) 0, 3, 10 or 30 mg/kg/day Acceptable/Guideline	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on decreased body weight gains and increased absolute and relative liver weights. **Developmental** NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on increased incidence of crooked hyoid.

Table 4. Subchronic, Chronic and Other Toxicity Tables		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800 Reproduction. Health and Envir- onmental Sciences, Study No.: TXT:K-030304-025, Dec. 27, 1988.	40952701(1988) Acceptable/Guideline 0, 5, 20 or 75 mg/kg/day.	**Parental/Systemic** NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based on increases in liver and kidney weight and presence of hepatic centrilobular diffuse hypertrophy. **Reproductive** NOAEL = 75 mg/kg/day. LOAEL = not observed - no effects a the highest dose tested. **Offspring** NOAEL = 20 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight and increased hepatic centrilobular vacuolation consistent with fatty changes in both sexes and generations.
870.4100a Chronic toxicity rodents	Refer to 870.4300 rat chronic feeding/carcinogenicity study below	
870.4100b Chronic toxicity dogs. DOW Chemical Co. Study # TXT:K-031304-029, Dec. 27, 1989.	41345401(1989) Acceptable/Guideline 0, 0.5, 3 or 15 mg/kg/day	NOAEL = 3 mg/kg/day LOAEL = 15] mg/kg/day based on increased alkaline phosphatase, cholesterol, absolute and relative liver weights and liver hypertrophy in both sexes.
870.4200. Carcinogenicity mice. Dow Toxicology Laboratory, Study No.: K-031304-027, July 23, 1990.	41651601 Not acceptable because inadequacy of dosing. 0, 5, 25 and 75 mg/kg/day.	The Carcinogenicity Peer Review Committed determined that the high dose in this study was not adequate for carcinogenicity evaluation.
8704300. Combined chronic feeding and carcinogenicity study - rats Health and Environmental Science, Study No.: TXT:K-031304-023, Dec. 26, 1989	41345403 (1989) 0, 5, 20 or 60 mg/kg/day. Acceptable/Guideline	NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based on decreased body weight gain in males. Increase in kidney tumors related to the alpha 2μ globulin model (not relevant to humans).
Gene Mutation 870.5100. Ames test. Microtest Research, Study No.: DCE 3/S/S5/AF2, January 18, 1985.	Accession No.: 259818. (1985) Acceptable (W. Woodrow reviewer)	No evidence of mutagenic activity in strains TA-97, TA-98, TA-100 and TA 1535 in the presence or absence of activation.
Cytogenetics 870. 5300. Mammalian gene mutation. Health and Environmental Sciences, Study No.: TXT:K-031304-022, August 1986.	MRID No.: 00163805. Acceptable (W. Dykstra reviewer).	Negative for genotoxic effect in the presence (up to 200 μg/mL) and absence (up to 100 μg/mL) of S9 in an *in vitro* mammalian gene mutation test with cultured (CHO/HGPRT) cells.

Table 4. Subchronic, Chronic and Other Toxicity Tables		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Cytogenetics 870.5375. Micro-nucleus test. Microtest Research Ltd. Study No.: DCE 3/MNT/ AR/KF11, March 13, 1985.	Accession No.: 259818. Acceptable (W. Woodrow reviewer).	No evidence of mutagenic potential in the mouse micronucleus test at a dose of 800 mg/kg.
Other Effects 870.5550. Unscheduled DNA synthesis. DOW Chemical Co.. No study number provided, June 5, 1982.	MRID No.: 00109456. Acceptable (W. Woodrow)	No increase in unscheduled DNA synthesis in the rat hepatocyte UDS assay at up to 10^{-4} moles/liter.
870.6200a Acute neurotoxicity screening battery	No studies available and not required.	
870.6200b Subchronic neurotoxicity screening battery		
870.6300 Developmental neurotoxicity		
870.7485 Metabolism and pharmacokinetics DOW Chemical Co. Study No.: K031304, August 11, 1987.	40305501 (1987). Acceptable/Guideline: Doses tested: 1 or 60 mg/kg.	Total recovery ranged from 94.81% to 99.24%. Radio-labeled nitrapyrin was rapidly absorbed (T1/2 = 1.2 to 3.2 hours and excreted in urine (~80 to 86%) with excretion essentially complete by 72 hours; < 1% remained in the tissues. 6-chloropicolinic acid and its glycine conjugate identified as urinary metabolites.
870.7485. Metabolism study in mice. Health and Environmental Research Labs. Study No.: 971119, Sept. 30, 1998.	44679301 (1998) Acceptable-Guideline Doses tested:25 or 250 mg/kg.	Mean total recovery was 99.38 to 100.82%. && to 83% absorbed based on urinary excretion. < 1% remained in tissues at 72 hours. Four distinct urinary metabolites detected by HPLC: 6-chloropicolinic acid (6-CPA), 6-CPA-glycine conjugate, CPA-taurine conjugate and parent (in high dose group only - possibly indicating saturation of metabolism).
870.7600 Dermal penetration Dow health and Environmental Research Laboratories, Study No.: HET K-031304-039, March 25, 1997.	44282501 radiolabeled nitrapyrin. Acceptable/Non-guideline	~26±6.4% recovered in the excreta in 24 hours. ~34.6±11% recovered after a total of 72 hours. Overall an estimate of dermal absorption in up to 46%.

Table 4. Subchronic, Chronic and Other Toxicity Tables		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Special studies	None with parent. It is noted that there are toxicity studies with the metabolite 6-CPA.	

*This study demonstrated hepatic hypertrophy and liver weight change at 200 mg/kg/day and the original review indicated 200 mg/kg/day as a LOEL. However, consistent with current HED guidance, liver hypertrophy and weight change alone do not constitute an adverse effect and therefore the NOAEL and LOAEL were set at 200 and 300 mg/kg/day.

3.3 Dose Response Assessment

Acute Dietary Endpoint: An acute endpoint was not identified for the general population including infants and children, because no effect were observed which could be attributed to a single dose exposure.

Chronic Dietary Endpoint: The chronic RfD of 0.03 mg/kg/day is derived from a NOAEL of 3.0 mg/kg/day based on liver effects at 15 mg/kg/day (LOAEL) in the chronic dog carcinogenicity study. A 100-fold uncertainty factor (10X inter-species extrapolation and 10X intra-species variability) is required. Since the special FQPA SF has been reduced to 1X, the chronic PAD is equal to the chronic RfD.

Carcinogenicity: Nitrapyrin is classified as "likely to be a human carcinogen" based on the mouse study which demonstrated liver, stomach, epididymal and Harderian gland tumors. The Q1* was determined to be 4.25×10^{-2} human equivalents. This classification was reaffirmed on February 9, 2005 following a revisit to the CARC where all of the issues raised by the DOW Company in their SAG review were considered. However, the CARC agreed that the Harderian gland tumors were no longer considered a response to treatment and the forestomach tumors not relevant to human health risk assessment. However, the CARC retained its concern for the epididymal tumors and did not accept the SAG proposed mechanism for liver tumors.

Incidental Oral: Because there is no proposed residential uses, endpoints selected for incidental oral exposure were not used in this assessment.

Dermal Absorption Factor: The HIARC did not select the 21-day dermal toxicity study in rabbits for this risk assessment because of the concern for hepatic toxicity seen following oral exposures in mice, rats, rabbits, and dogs after various durations of exposures. In addition, the apparent low absorption via the dermal route, which was not demonstrated in the dermal rabbit study, would indicate that the rabbit is a poor model for assessing dermal toxicity. A ratio of the oral LOAEL 30 mg/kg/day from the developmental study in rabbits to the dermal LOAEL = 1000 mg/kg/day, based on a common endpoint (hepatic toxicity), yields a dermal absorption value of 3% whereas a dermal absorption study in rats indicate 46% dermal absorption at 24 hours. Therefore, the rat is a better model for dermal risk assessment of this chemical. Since an oral NOAEL was selected, 46% dermal absorption should be used

for route-to-route extrapolation. A dermal absorption value of 46% was calculated to represent the residual chemical that could be absorbed and for use in route-to-route extrapolation.

Short-Term (1-30 days) and Intermediate-Term (1-6 months) Dermal and Inhalation Endpoints: Short- and intermediate-term occupational dermal and inhalation endpoints of concern were identified. The occupational short-term dermal and inhalation endpoint (10 mg/kg/day) is from a developmental oral study in rabbits and is based on liver weight effects. The intermediate-term dermal and inhalation endpoint (3 mg/kg/day) is from a chronic dog study and is also based on liver effects. A dermal penetration/absorption study was available for nitrapyrin.

Long- Term (> 6 months) Dermal and Inhalation Endpoints: Long-term occupational inhalation and dermal endpoints were not identified since there are no long-term activities associated with nitrapyrin.

MOE for Occupational Risk Assessment: For occupational short-, intermediate-, and long-term dermal and inhalation exposure risk assessments, an MOE (Margin of Exposure) of greater equal to 100 is adequate. The target MOE for occupational exposure is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation). Because endpoints are the same for both dermal and inhalation exposure, the individual dermal and inhalation MOEs should be combined into a total MOE for comparison to the target MOE.

MOE for Residential Risk Assessment: No residential uses are established or proposed for nitrapyrin.

Table 5. Endpoints Selected by HIARC for Assessing Occupational and Residential Risks for Nitrapyrin

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary - all populations.	An appropriate endpoint attributable to a single dose was not identified.		
Chronic Dietary (All populations)	NOAEL= **3** mg/kg/day UF = 100 **Chronic RfD** = **0.03** mg/kg/day	FQPA SF = 1 X **cPAD** = chronic RfD / FQPA SF = 0.03 mg/kg/day	Chronic feeding - dog LOAEL = 15 mg/kg/day based on liver effects.
Short-Term Incidental Oral (1-30 days)	Maternal NOAEL= 10 mg/kg/day	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** = NA	Developmental toxicity - rabbits. LOAEL = 30 mg/kg/day based on body weight and liver weight effects.
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= 3 mg/kg/day	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** = NA	Chronic feeding - dog LOAEL = 15 mg/kg/day based on liver effects.

Table 5. Endpoints Selected by HIARC for Assessing Occupational and Residential Risks for Nitrapyrin			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Short-Term Dermal [a] (1 to 30 days)	Oral Maternal NOAEL= 10 mg/kg/day	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Developmental toxicity - rabbits. LOAEL = 30 mg/kg/day based on body weight and liver weight effects.
Intermediate-Term Dermal [a] (1 to 6 months)	Oral NOAEL= 3 mg/kg/day	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** LOC for MOE =100	Chronic feeding - dog LOAEL = 15 mg/kg/day based on liver effects.
Long-Term Dermal [a] (> 6 months)	Oral NOAEL = 3 mg/kg/day	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Chronic feeding - dog LOAEL = 15 mg/kg/day based on liver effects.
Short-Term Inhalation [b] (1 to 30 days)	Oral NOAEL= 10 mg/kg/day (inhalation absorption rate = 100%)	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Rabbit developmental toxicity LOAEL = 30 mg/kg/day based on body and liver weight effects.
Intermediate (1 to 6 months) and long term (> 6 months) [b]	Oral NOAEL = 3 mg/kg/day (inhalation absorption rate = 100%)	FQPA SF = 1 X **Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Chronic feeding - dog LOAEL = 15 mg/kg/day based on liver effects.
Cancer (oral, dermal, inhalation)	Classified as "likely to be a carcinogen in humans" Q_1^* is 4.25×10^{-2} $(mg/kg/day)^{-1}$		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable,

a= low absorption via the dermal route, which was not demonstrated in the dermal rabbit study, would indicate that the rabbit is a poor model for assessing dermal toxicity. A ratio of the oral LOAEL 30 mg/kg/day to the dermal LOAEL = 1000 mg/kg/day, based on a common endpoint (hepatic toxicity), yields a dermal absorption value of 3% whereas a dermal absorption study in rats indicate 46% dermal absorption at 24 hours. Therefore, the rat is a better model for dermal risk assessment of this chemical.

b= Absorption via the inhalation route is presumed to be equivalent to oral absorption (100%).

3.4 ENDOCRINE DISRUPTION

Evidence of endocrine disruption due to nitrapyrin was not observed in the studies reviewed. EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTACs recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, nitrapyrin may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Nitrapyrin can be applied with ground equipment using broadcast, soil band treatment, soil incorporated broadcast treatment, top dressing equipment, soil injection and soil sidedress. The only soil side dress application is for corn and is allowed up to 30 days after planting. The registrant, Dow Agro Science is supporting use of nitrapyrin on corn, sorghum and wheat. The nitrapyrin labels indicate that use of this pesticide is limited to licenced operators and the product is not available to homeowners.

4.2 Dietary Exposure/Risk Pathway

The nature of the residue has been adequately determined for current uses in corn, sorghum and wheat; but because submitted metabolism studies have been limited to corn, additional studies will likely be required should it be desired to register this chemical on other crops. Residues in cereal plants are much higher in the stems and leaves than in the grains. Since NP is only soil applied, all residues in plants must be translocated from the soil. The residue consists almost completely of free and conjugated 6-chlorpicolinic acid. Nitrapyrin, per se, was not found.

Acceptable field studies have also been performed to support the uses on these three crops and adequate stability studies support the results of these studies. The field studies support the revised tolerances shown in the tolerance table. Tolerances on the grains are currently based on the lower limit of the method. A new tolerance for wheat grain is recommended at 0.5 ppm based upon re analyses

performed later that found actual residues. Tolerance on wheat forage and straw were also at 0.5 ppm, but upon re-analysis were proposed to be revised to 2 ppm and 6 ppm, respectively (C. Olinger, 6 August, 1992, D175884, D175861 and D 175854). Tolerances for corn and sorghum, forages, straw, etc, currently range from 0.5 to 1.0 ppm.

Acceptable processing studies have also been performed for commodities of all three crops and adequate stability studies support the results of these processing studies. Recommended new tolerances of 2.0 ppm for wheat, milled byproducts and 0.2 ppm for corn, milled byproducts are based upon these processing studies where concentration of residues occurred.

The nature of the residue also been adequately determined in livestock and adequate feeding studies have also been performed. From the metabolism studies and the feeding studies, HED has determined there is no reasonable expectation of residues in meat, milk, poultry or eggs given current uses. Existing tolerances on these commodities should be removed. If uses on additional crops are requested that might result in residues in meat, milk, poultry and eggs, additional data on livestock and poultry may be required.

The nature of the residue in rotational crops has been adequately determined, and a rotational crop field study has been completed that is adequate so long as currently labeled plant back intervals greater than 1 year are retained. If shorter plant back intervals are requested, in some cases additional rotational crop field trials may be needed.

Adequate tolerance enforcement methods exist for residues in corn, wheat and sorghum. Since there is no reasonable expectation of residues in livestock or poultry, no methods are required for tolerance enforcement in these animal derived commodities. However, should new uses of nitrapyrin be requested that lead to higher residues in livestock or poultry, additional data may be required to support a tolerance enforcement method for livestock. Nitrapyrin has been shown to be recovered and detected through the PAM I multiresidue protocol. 6-CPA has also been tested through the PAM I protocol and was not recovered.

Tolerances are currently established in for nitrapyrin, expressed as nitrapyrin and 6-CPA, in corn, sorghum, wheat and in livestock tissues and milk. The nitrapyrin team recommends that these tolerances be more articulately expressed as nitrapyrin plus free and conjugated residues of 6-CPA. This does not affect the concentrations used to calculate tolerances because they based upon measurement of hydrolysates yielding free plus conjugated residues.

The current labels are adequate for residue chemistry purposes.

4.2.1 Residue Profile

Nitrapyrin is used almost entirely on corn, with less than 1% used on sorghum and wheat. Nitrapyrin currently has tolerances on wheat, corn and sorghum in 40 CFR 180.350. Because studies submitted since the last Registration Standard have shown higher residues, new tolerances are recommended for wheat, for some crop fractions of wheat, and for one crop fraction of corn. In addition, there is no reasonable expectation of residues in livestock or poultry, and HED recommends that the current tolerances on these products, based upon non-detectable residues, should be removed, so that residues in livestock, poultry, eggs and milk are not included in this assessment.

Residues of concern for risk assessment for treated crops and rotated crops are parent nitrapyrin and free and conjugated forms of its 6-chloropicolinic acid (6-CPA) metabolite. (Review of Nitrapyrin Metabolism by the nitrapyrin Team on 3 March 2004, in process, DP Barcode D299923). Analytical methods are adequate for tolerance enforcement and risk assessment purposes.

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 1.3), and the Lifeline Model Version 2.0 which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support the reregistration eligibility decision for nitrapyrin.

This is a refined chronic dietary assessment. Actual field trial data were used for most corn, sorghum and wheat commodities with a best estimate (see below) of the percent crop treated. Tolerance level residues were used for some processed fractions of wheat. Tolerance levels for field corn were the same as the lower limit of quantification of the method used in the field trials. Livestock and poultry were not included because HED is recommending that tolerances on animal commodities be removed based upon no reasonable expectation of residues in these commodities.

Residue Information

Input residue information are shown in Table 6. Monitoring data are not available for nitrapyrin or for 6-CPA. Actual field trial data were used for all fresh commodities. Proposed tolerances were used for a couple of processed commodities. Percent crop treated values were used in these assessments. The usual agencies do not collect usage information on nitrapyrin, however, OPP has concluded that the usage information provided by the registrant was reasonable for use in this assessment: 8% crop treated on corn, <1% crop treated on wheat and <1% crop treated on sorghum. Processing factors were used for corn meal and corn flour, and the factor for corn flour was also applied to corn starch. A corn, milled fractions, factor was applied to corn bran. A processing factor of 1.0 was used for corn oil and corn syrup. A processing factor was also used for wheat flour, but the recommended tolerance was used for wheat bran (3.0 ppm) and the recommended milled fraction tolerance (2.0 ppm) for wheat germ. No processing factors were used for sorghum commodities in the assessment. To be conservative, a factor of 1.1 was used for processing of whole sweet corn cobs into sweet corn kernels.

Table 6. Data and Residue Estimates Used in Dietary Analyses

RAC	Food Forms	Tolerance or field trial average	%CT	Processing Factors
Corn	Flour	0.1	8	0.55
	Oil	0.1	8	1
	Starch	0.1	8	0.55
	Syrup	0.1	8	1
	meal	0.1	8	1.09
	bran	0.1	8	1.29
Sweet Corn		0.06	8	1
	kernels	0.06	8	1.1
sorghum	grain	0.1		1
	molasses	0.1	1	1
wheat	grain	0.18	1	1
	flour	0.18	1	0.37
	germ	2.0	1	1
	bran	3.0	1	1

4.2.2 Acute Dietary Exposure and Risk

No end point was selected for the acute dietary exposure scenario since neither the rat or rabbit demonstrated definite toxicity following a single dose and developmental toxicity was not a concern for nitrapyrin; therefore, no acute dietary assessment is included.

4.2.3 Chronic Dietary Exposure and Risk

A refined chronic dietary exposure assessment was performed in order to determine the exposure risk assessment to nitrapyrin for use in chronic dietary risk assessment from all registered uses. The assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. Field trial data, estimated percent crop treated information, and processing factors, where available, were used. The chronic and cancer dietary exposure estimates were also conducted using the Lifeline™ model (Version 2.0). These Lifeline™ assessments were also conducted using the same consumption data as the DEEM-FCID™ (CSFII, 1994-1996 and 1998 consumption data with FCID). Lifeline™ uses the recipe file to relate RACs to foods "as-eaten" (D299299, March 04, D Soderberg).

For all commodities, the results of both the DEEM-FCID™ and Lifeline™ analyses for chronic dietary exposure (food only) yielded exposure results <1% cPAD for the US Population and for all population subgroups, which is below HED's level of concern. Dietary exposure results <100% of the cPAD are below HED's level of concern. Summary of chronic dietary risk estimates are presented in table 7.

Table 7. Summary of Chronic Dietary Exposure and Risk for Nitrapyrin

Population Subgroup	Chronic Dietary Exposure and Risk			
	DEEM		Lifeline	
	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000013	<1	0.000012	<1
All Infants (< 1 year old)	0.000015	<1	0.000012	<1
Children 1-2 years old	0.000027	<1	0.000026	<1
Children 3-5 years old	0.000031	<1	0.000029	<1
Children 6-12 years old	0.000023	<1	0.000021	<1
Youth 13-19 years old	0.000017	<1	0.000015	<1
Adults 20-49 years old	0.000011	<1	0.000011	<1
Adults 50+ years old	0.000007	<1	0.000019	<1
Females 13-49 years old	0.000012	<1	0.000014	<1

4.2.4 Cancer Dietary Exposure and Risk

A cancer dietary risk assessment was not conducted because exposure to nitrapyrin, per se, in the diet is negligible (zero) and the cancer endpoint is relevant only to nitrapyrin, per se, and not to 6-CPA. Please see section 5.3 (DWLOCs for Cancer) for an assessment of aggregate cancer risk from drinking water exposures to nitrapyrin.

4.3 Water Exposure/Risk Pathway

The Environmental Fate and Effects Division (EFED) (D299121, A. Al-Mudallal, 4/14/04) provided estimated environmental concentrations (EECs) of nitrapyrin and it's major degradate 6-chloropicolinic acic (6-CPA)for use in the human health risk assessment.

Potential human exposure to parent nitrapyrin and it's major degradate 6-chloropicolinic acid (6-CPA) from ingestion of drinking water was assessed by modeling because there are no monitoring data for nitrapyrin and 6-CPA in surface and ground water. EFED decided to model nitrapyrin and 6-CPA separately because a combined residue approach was not possible. 6-CPA was not detected or

adequately quantified in all environmental fate studies that are used in the PRZM/EXAMS input parameters. Therefore, no combined residue half-lives (nitrapyrin + 6-CPA) could be determined.

Tier II PRZM-EXAMS modeling was performed using index reservoir (IR) scenarios with percent crop area (PCA) adjustment factors for the use of nitrapyrin on corn, sorghum, and wheat. The application rate for corn is 0.5 lbs ai/acre with 2 applications at a 30 day interval. The application rate for sorghum and wheat is 1.0 lbs ai/acre with 1 application. For 6-CPA modeling, the application rate was corrected for the difference in molecular weight between parent nitrapyrin and 6-CPA. Due to the lack of environmental fate data for 6-CPA (with the exception of the aged residue-batch equilibrium data), EFED assumed that the degradate 6-CPA is stable to all abiotic and biotic routes of degradation. This assumption produces conservative estimates of 6-CPA concentrations in drinking water.

The default PCA factor of 0.87 was used in the modeling to reflect the possibility of having more than one crop treated with nitrapyrin within the same water shed. Figure 1 shows the percentage use of nitrapyrin in the United States. Table 8 presents the model estimated concentrations of nitrapyrin and 6-CPA in surface water.

The Texas sorghum scenario produced the highest estimated concentration of nitrapyrin in surface water among the modeled scenarios. The estimated concentration of nitrapyrin in water is not expected to exceed 1.21 ppb for the 1 in 10 year annual peak concentration, 0.03 ppb for the 1 in 10 year annual daily mean concentration, and 0.01 ppb for the 30 year annual average concentration. The Oregon wheat scenario produced the highest estimated concentration of 6-CPA in surface water among the modeled scenarios. The estimated concentration of 6-CPA in water is not expected to exceed 1.71 ppb for the 1 in 10 year annual peak concentration, 1.63 ppb for the 1 in 10 year annual daily mean concentration, and 1.02 ppb for the 30 year annual average concentration.

For drinking water originating in ground water, the SCI-GROW model provided estimated concentration values ranging between 30 and 278 µg/L for 6-CPA, and 0.07 ug/L for nitrapyrin to evaluate the risk to human health.

For drinking water risk assessment, HED estimated chronic drinking water exposures using 1.6 ug/L of 6-CPA in surface water and 31-280 ug/L 6-CPA in groundwater. HED estimated cancer risks from drinking water exposures to nitrapyrin at 0.01 ug/L in surface water and 0.07 ug/L of nitrapyrin in ground water. HED used 6-CPA residues in drinking water to estimate chronic risk because the chronic effects have been determined to be relevant to both nitrapyrin and 6-CPA, and as the major soil and water degradate of nitrapyrin residues of 6-CPA represent the worst-case exposure scenario. HED used residues of nitrapyrin to estimate cancer risk, because the tumors seen in lab animals from toxicity testing have been determined to be relevant to exposure to nitrapyrin, per se, and not 6-CPA.

There are several uncertainties and assumptions in the water assessment of nitrapyrin and its degradate (6-CPA). Primary among these is 6-PA was not detected or adequately quantified in all environmental fate studies that are used in the PRZM/EXAMS input parameters. Therefore, no

combined residue half-lives (nitrapyrin + 6-CPA) could be determined. A conservative approach was used to generate the drinking water estimates of the concentrations of nitrapyrin and 6- CPA.

Table 8. Estimated Concentrations of Nitrapyrin and 6-CPA in Surface Drinking Water Using IR/PCA PRZM/EXAMS Scenarios

Crop Scenario	1 in 10 year peak concentration ppb		1 in 10 year annual daily average concentration ppb		30-year annual daily average ppb	
	Corn					
	Nitrapyrin	6-CPA	Nitrapyrin	6-CPA	Nitrapyrin	6-CPA
Florida Corn	0.595	0.839	0.024	0.175	0.010	0.077
Illinois Corn	0.525	0.590	0.020	0.250	0.011	0.130
Mississippi Corn	0.435	0.938	0.009	0.295	0.003	0.128
North Carolina Corn	0.490	0.624	0.019	0.208	0.010	0.114
North Dakota Corn	0.406	0.794	0.015	0.551	0.006	0.324
Ohio Corn	0.335	0.545	0.014	0.241	0.009	0.154
Oregon Corn	0.208	0.381	0.005	0.126	0.002	0.050
Pennsylvania Corn	0.158	0.568	0.005	0.359	0.001	0.134
Texas Corn	0.868	1.182	0.024	0.374	0.014	0.194
Sorghum						
Kansas Sorghum	0.685	0.944	0.020	0.338	0.009	0.165
Texas Sorghum	1.214	1.431	0.032	0.459	0.014	0.236
Wheat						
North Dakota Wheat	0.451	0.743	0.011	0.489	0.005	0.286
Oregon Wheat	0.343	1.705	0.011	1.627	0.004	1.023
Texas Wheat	1.057	0.781	0.026	0.260	0.010	0.117

4.4 Residential exposure/Risk Pathway

No residential use identified on nitrapyrin labels.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

An aggregate risk assessment is defined as the evaluation of the likelihood of the occurrence of an adverse health effect resulting from exposure to a single substance via all relevant routes. The current uses for nitrapyrin encompass only agricultural use sites; there are no non-occupational (residential) uses. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered.

Under OPP's aggregate risk assessments for nitrapyrin, HED has compared estimates of concentrations of nitrapyrin in drinking water to Drinking Water Levels of Comparison (DWLOCs). A DWLOC is the portion of the acute PAD or chronic PAD remaining after estimated dietary (food only) exposures have been subtracted and the remaining exposure has been converted to a concentration (ppb). This concentration value (DWLOC) represents the available or allowable exposure through drinking water for nitrapyrin.

Under the chronic risk assessment, the remaining portion of the chronic PAD is based on average dietary exposures for each relevant population subgroup considered. DWLOC values vary for population subgroups depending on dietary exposure through foods for each subgroup, and the assumptions made about drinking water consumption, and body weights for each subgroup.

DWLOCs are theoretical upper limits on a pesticide's concentration in drinking water that are used to determine how much of the acceptable exposure is available for exposure through drinking water. OPP uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. DWLOC values are not regulatory standards for drinking water; however, they do have regulatory impact through aggregate exposure and risk assessments.

5.1 DWLOCs for Acute Exposure

An acute RfD was not selected for nitrapyrin because an appropriate endpoint attributable to a single dose was not available from any study including the developmental toxicity studies, therefore no assessment is included. (John Doherty, March 2004).

5.2 DWLOCs for Chronic Exposure

A chronic dietary NOAEL of 3 mg/kg/day was selected for nitrapyrin (J. Doherty, March 2004). This NOAEL was used to calculate the chronic DWLOCs. An uncertainty factor of 100 was applied based on a 10x for intraspecies variation and a 10x for interspecies extrapolation. Therefore, the theoretical chronic RfD or the theoretical Chronic Population Adjusted Dose(cPAD) would be 0.03 mg/kg/day. The default body weights and daily water consumption values were applied for each target population (i.e., U.S. population, children 1-6, and infants). Default body weights and consumption values for calculation of the DWLOCs were: 2L/70 kg (adult male), 2L/60 kg (adult female) and 1L/10 kg (children and infants), respectively.

The chronic EECs (highest value) generated by EFED are less than HED's calculated chronic DWLOCs for 6-CPA and nitrapyrin in drinking water. The chronic DWLOCs range from 300 µg/L for the population subgroup with the highest food exposure (Children 1 to 2 years old) to 1050 µg/L for the subgroups U.S. Population, Adults 20 to 49 years old, and Adults 50+ years old. HED thus concludes with reasonable certainty that residues of nitrapyrin in drinking water will not contribute significantly to the aggregate chronic human health risk, and that the chronic aggregate exposure from nitrapyrin residues in food and drinking water will not exceed the Agency's level of concern (100% of the chronic PAD) by any population subgroup.

Table 9. Summary of Chronic DWLOC Calculations for Nitrapyrin and 6 CPA

Population Subgroup[1]	Chronic Scenario					
	Theoretical cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[1]	6-CPA Surface Water EDWC (µg/L)	6-CPA Ground Water EDWC (µg/L)	Chronic DWLOC (µg/L)[2]
General U.S. Population	0.03	0.000013	0.029987	1.6 (Wheat) 0.55 (Corn) for CPA	30-280 for CPA	1050
All Infants (< 1 year old)		0.000015	0.029985			300
Children 1-2 years old		0.000027	0.029973			300
Children 3-5 years old		0.000031	0.029969			300
Children 6-12 years old		0.000023	0.029977			300
Youth 13-19 years old		0.000017	0.029983			900
Adults 20-49 years old		0.000011	0.029989			1050
Adults 50+ years old		0.000007	0.029993			1050
Females 13-49 years old		0.000012	0.029988			900

[1] Maximum Chronic Water Exposure (mg/kg/day) = [Chronic PAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]

[2] Chronic DWLOC(µg/L) = $\frac{\text{[maximum chronic water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

Consumption = 1 L/day for populations <13 years old and 2 L/day for populations ≥ 13 years old. Default body weights = 70 kg for adults > 20 years old and general U.S. population, 60 kg for females ≥ 13 years old and youth 13-19 years old, and 10 kg for all others. Values are rounded to 2 significant figures.

As shown in Table 9, the adult male and female populations as a whole had chronic DWLOC values that exceed the surface and ground water EECs for 6- CPA and nitrapyrin, consequently, the Agency concludes with reasonable certainty that there is no drinking water risk of concern for these populations exposure to nitrapyrin or 6 CPA. Chronic DWLOCs values derived for infants and children also exceeded the chronic EECs for ground water and surface water are, also of no concern to the Agency.

Note: 6-CPA values are shown in Table 9 because they are higher than EECs for nitrapyrin, and represent the worst-case for exposure to residues of nitrapyrin.

5.3 DWLOCs for Cancer

For the cancer (Q_1*) exposure calculations, the Agency used multi-year mean water concentration values. The $DWLOC_{cancer}$ is the concentration in drinking water as a part of the aggregate chronic exposure that results in a negligible cancer risk (10^{-6}).

An aggregate cancer risk assessment for the U.S. Population based on nitrapyrin was conducted in which food exposure was assumed to be negligible but water exposures were not. The EECs used for the cancer aggregate risk assessment are 0.01 ug/L (surface water) and 0.07 ug/L (groundwater). The calculated cancer DWLOC is 0.84 ug/L. Since the model-based estimates for allowable concentrations of nitrapyrin in surface water and ground water are below the calculated cancer DWLOC, HED concludes that aggregate exposure to nitrapyrin in food and drinking water will not result in a cancer risk of concern.

The cancer risk is presented in Table 10.

Table 10. Summary of Cancer DWLOC Calculations for Nitrapyrin

Population	Q*	Negligible Risk Level[1]	Target Max Exposure[2] mg/kg/day	Chronic Food Exposure mg/kg/day	Max Water Exposure[3] mg/kg/day	Surface Water EDWC (μg/L)	Ground Water EDWC (μg/L)	Cancer DWLOC[4] (μg/L)
U.S. Pop	4.25e-02	1.0e-06	0.000024	NA	0.000024	0.01 (corn)	0.07	0.84

[1] $DWLOC_{CANCER}$ was calculated for U.S. population only. Default body weights and consumption values for calculation of the DWLOCs were: 2L/70 kg

[2] Target Maximum Exposure (mg/kg/day) = [negligible risk/Q*]

[3] Maximum Water Exposure (mg/kg/day) = [Target Maximum Exposure - (Chronic Food Exposure + Residential Exposure (Lifetime Average Daily Dose))]

[4] Cancer DWLOC(μg/L) = $\frac{[\text{maximum water exposure (mg/kg/day)} \times \text{body weight (kg)}]}{[\text{water consumption (L)} \times 10^{-3}\ \text{mg/μg}]^2}$

6.0 CUMULATIVE RISK

Because of the selective activity to azotobacter, nitrapyrin can be used as an nitrogen nitration inhibitor and soil bactericide, and can delay the nitration of ammonium ion in soil when used together with urea and nitrogen fertilizer. It is the only chemical in this class of compounds. For the purposes of this risk assessment, therefore, EPA has not assumed that nitrapyrin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism

determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 Occupational Exposure

HED has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during standard uses associated with nitrapyrin. There is a low potential for occupational post-application exposure when a soil directed pesticide is used. Nitrapyrin is applied to the soil directly and is soil incorporated well before the plants are mature. Further, the timing of the application greatly reduces the potential for post application exposure to treated soil. Also, many agricultural operations mechanically plant seeds early in the season, which minimizes the potential for contact. Significant exposure during harvesting or any other late season activities, is not likely since the chemical is applied pre-plant.

7.1 Occupational Handler

The Agency has found that occupational exposure to nitrapyrin via the dermal and inhalation routes of exposure may occur during mixing, loading and applying through the use of ground spray. Based on the use patterns, 2 major occupational exposure scenarios were identified for nitrapyrin: (1) mixing/loading liquids for groundboom application (2) application of sprays via groundboom application.

Since the use patterns for nitrapyrin do not suggest any long term use, exposure scenarios of a longer duration were not considered. For non-cancer assessment the exposure scenarios are of short-term (1-30 days) and intermediate-term (1 to 6 months). The estimated exposures considered baseline protection (long pants, long shirts and no gloves - dermal; no respirator - inhalation) and additional PPE (long pants, long shirts and chemical resistant gloves). For cancer assessment the estimated risk considered baseline protection (long pants, long sleeved shirts and no gloves - dermal; no respirator - inhalation) and additional PPE (long pants, long sleeved shirts and chemical resistant gloves and/or double layer of clothing - dermal; all of the dermal protection plus 90% protection from organic vapor respirator - inhalation), and engineering controls (closed mixing and loading system). Handler exposure assessments were completed by EPA using baseline exposure scenarios previously noted and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an MOE of 100 for non-cancer risks. For cancer, there is a concern for risk estimates $>1.0 \times 10^{-4}$.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted to the Agency in support of the reregistration of nitrapyrin. In such instances, it is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available. HED's level of confidence in these data are shown in the occupational and residential exposure assessment and recommendations for nitrapyrin (S.Tadayon, 2004).

7.2 Noncancer Handler Exposure/Risks

The short-term MOEs for dermal and inhalation exposures were calculated using an oral NOAEL of 10 mg/kg/day for both exposure pathways and the intermediate -term MOEs for dermal and inhalation exposures were calculated using an oral NOAEL of 3 mg/kg/day.(see Section 3.3 Dose Response Assessment). The Agency also used route-to-route extrapolations from these oral studies for exposure assessments. A dermal absorption rate of 46% was applied to the dermal exposure assessments and an inhalation absorption rate of 100% was applied to the inhalation exposure assessments.

The results of the short and intermediate-term handler assessments are presented in Table 11 and indicate that all potential non-cancer exposure scenarios provide a total MOE(s) greater than or equal to 100 at either the baseline (i.e., long pants, long sleeved shirts, no gloves) using open systems or PPE (i.e., long pants, long sleeved shirts, and chemical resistant gloves while using open systems). The result of short and intermediate -term inhalation MOE for all scenarios range from 880 to 4100 and short and intermediate -term dermal MOE for all scenarios range from 1 to 420. Dermal exposure rather than inhalation exposure drives the total MOE for all scenarios. Four MOEs were calculated and total MOEs for all scenarios range from 1 to 420. The data show that baseline or mitigation measures raised the MOEs to values greater than or equal to 100 for all scenarios.

Table 11. Summary of Occupational Handler Risk for Nitrapyrin

Exposure Scenario (Scenario #)	Crop	Application Rate lb ai/A	Daily Area Treated A/day	Total Baseline Short-Term MOE	Total Baseline Intermediate-Term MOE	Total PPE Short-Term MOE	Total PPE Intermediate-Term MOE
Mixer/Loader							
Mixing/Loading Liquids for Groundboom application (1)	Wheat, Corn, Sorghum	1	200	3	1	250 (gloves)	100 (gloves)
Applicator							
Sprays for Groundboom application (2)	Wheat, Corn, Sorghum	1	200	420	150	420	150

Baseline dermal attire scenarios includes long pants, long sleeved shirts and no gloves.
Baseline inhalation attire represents no respirator
PPE1 dermal attire includes long pants, long sleeved shirts and gloves for mixer/loaders only.

7.3 Cancer Handler Exposure/Risks

The cancer risk assessments for handlers used baseline exposure scenarios and, as needed, increasing levels of risk mitigation (PPE and engineering) to achieve cancer risks that would be considered of no concern. According to Agency policy, acceptable cancer risks for occupational exposure to pesticides varies from 1×10^{-4} to 1×10^{-6}, depending on the course of action taken by the Agency as outlined in the policy memo on this subject. The Q_1* used in this risk assessment is 4.25×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents. Potential cancer risks Lifetime Average Daily Dose (LADD) to handlers were assessed using the following assumptions:

- The average body weight of 70 kg is used, representing a typical adult.
- Career duration is assumed to be 35 years. This represents a typical working lifetime.
- Lifetime is assumed to be 70 years.
- Dermal absorption is assumed to be 46%, and inhalation absorption is assumed to be 100% of the oral dose. The dermal and inhalation MOEs were added together to represent total MOEs.

In addition, two exposure frequencies were used in the calculations, the first represented the maximum number of applications per site per season to represent private use (3), and the second frequency applied a factor of ten to the first frequency to represent commercial handlers making multiple applications per site per season (30).

The results of the occupational handler cancer assessments presented in Table 12 indicate Cancer risks for occupational dermal and inhalation exposures range from 6.66×10^{-3} to 3.6×10^{-6} at the baseline (long pants, long sleeved shirts and no gloves), 5.58×10^{-5} to 3.6×10^{-6} PPE1(long pants, long sleeved shirts and gloves), 4.4×10^{-5} to 2.90×10^{-6} at PPE2 (long pants, long sleeved shirts, double layer and gloves and no respirator), 3.96×10^{-5} to 2.6×10^{-6} at PPE3 (long pants, long sleeved shirts, double layer, gloves and organic vapor respirator), and 2.02×10^{-5} to 1.20×10^{-6} at engineering control. Overall, these data suggest that none of the evaluated scenarios have cancer risks that exceed 1.00×10^{-4} (the Agency's level of concern for occupational cancer risk begins at $\leq 1.00 \times 10^{-4}$ with all attempts to mitigate risks to $\leq 1.00 \times 10^{-6}$, when possible).

Table 12: Occupational Handler, Summary of Cancer (Q*) Risk for Nitrapyrin

Exposure Scenario #	Application Rate lb ai/A	Acres treated A/day	Crop Type	Baseline Risk 3/30	PPE1 Risk 3/30	PPE2 Risk 3/30	PPE 3 Risk 3/30	E. control Risk 3/30
Mixer/Loader Exposure								
Mixing/Loading Liquids for Groundboom application (1)	1.00	200	Wheat, Corn, Sorghum	6.66e-4 /6.66e-3	5.88e-6 /5.88e-5	4.5e-6 /4.5e-5	3.96e-6 /3.96e-5	2.02e-6 /2.02e-5
Applicator								
Sprays for Groundboom application (2)	1.00	200	Wheat, Corn, Sorghum	3.6e-6 /3.6e-5	3.6e-6 /3.6e-5	2.9e-6 /2.9e-5	2.6e-6 /2.6e-5	1.2e-6 /1.2e-5

Baseline dermal unit exposure scenarios includes long pants, long sleeved shirts and no gloves.
PPE1 long pants, long sleeved shirts and gloves (no respirator)
PPE 2 cancer risk includes long pants, long sleeved shirts, double layer, gloves and no respirator.
PPE 3 cancer risk includes long pants, long sleeved shirts, double layer, gloves and organic vapor respirator.
Engineering Control dermal unit exposure scenarios includes long pants, long sleeved shirts, gloves.
Engineering inhalation unit exposure represents no respirator.
Two exposure frequencies were used for cancer, the first represented the maximum number of applications per site per season to represent private use (3), and the second frequency applied a factor of ten to the first frequency to represent commercial handlers making multiple applications per site per season (30).

7.4 Occupational Postapplication

There is a low potential for occupational post-application exposure when a soil directed pesticide is used. Nitrapyrin is applied to the soil directly and is soil incorporated well before the plants are mature. Further, the timing of the application greatly reduces the potential for post application exposure to treated soil. Also, many agricultural operations mechanically plant seeds early in the season, which minimizes the potential for contact. Significant exposure during harvesting or any other late season activities, is not likely since the chemical is applied pre-plant.

HED believes that there is negligible possibility of exposure and risk from uses of nitrapyrin that are applied to the soil or are soil "directed". This presumes workers will have no direct contact with residues in treated soil.

The Agency's requirements regarding Restricted-Entry Intervals (REIs) are included in the 40 CFR 156.208. Guidance on applying these requirements are also included in Chapter 11 of the Office of Pesticide Programs' Label Review Manual. In accordance with the 40 CFR 156.208, the REI is based on the acute toxicity of the "technical active ingredient material".

The toxicity categories of the active ingredient for acute dermal, eye irritation, and skin irritation potential are used to determine the interim REI. If one or more of the three acute toxicity effects are in toxicity category I, the interim REI is established at 48 hours. If none of the acute toxicity effects is in category I, but one or more of the three is classified as category II, the interim REI is established at 24 hours. The acute toxicity classification for primary eye irritation of nitrapyrin is category II which requires a 24-hour REI.

7.5 Incident Data

Relatively few incidents of illness have been reported due to nitrapyrin. Some of the reports suggest that nitrapyrin can be an eye and skin irritant (J Blondell April 2004).

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Toxicology

There are no data gaps for nitrapyrin at this time.
The issue of whether or not nitrapyrin is mutagenic in the Salmonella tests is not considered resolved since there is a weakly positive study reported by the NTP program but also a negative study provided by the DOW Company. In order to resolve the issue of a possible mutagenic concern, the CARC suggested that the DOW Company conduct another study with Salmonella typhimurium but include the preincubation modification of the plate test (considered more sensitive than the plate test).

The HIARC recommended that a 28 day inhalation toxicity study be conducted with nitrapyrin to provide a better endpoint for inhalation risk assessment. However, there are occasions when the requirement for inhalation toxicity studies should be waived for ethical or scientific reasons. If no significant inhalation hazard is identified during risk characterization and risk assessment, HED may recommend a waiver. The following criteria are presented to justify a waiver for an inhalation study:

1) low vapor pressure, 2.8×10^{-5} mm Hg .
2) the waxy physical nature of technical nitrapyrin precludes generating aerosols of appropriate atmospheric concentrations to meaningfully assess the inhalation toxicity.
3) dermal exposures drive occupational risks. Calculated inhalation MOEs for all scenarios range from 880 to 4100.
4) Can not be classified as to a specific inhalation tox category.
Please refer to the memo from M Stasikowski titled"*Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*"dated August 15, 2002.

8.2 Product and Residue Chemistry

NA

8.3 Occupational and Residential Exposure

NA

9.0 Tolerance Reassessment

Nitrapyrin is used almost entirely on corn, with less than 1% used on sorghum and wheat. Nitrapyrin currently has tolerances on wheat, corn and sorghum in 40 CFR 180.350. Because studies submitted since the last Registration Standard have shown higher residues, new tolerances are recommended for wheat, for some crop fractions of wheat, and for one crop fraction of corn. In addition, there is no reasonable expectation of residues in livestock or poultry, and HED recommends that the current tolerances on these products, based upon non-detectable residues, should be removed, so that residues in livestock, poultry, eggs and milk are not included in this assessment. A Tolerance Summary is presented in table 13.

Table 13. Tolerance Summary for Nitrapyrin

Commodity	Established/Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Corn, Field, Grain	0.1 ppm	0.1 ppm	Corn, Field, Grain
Corn, Sweet, K+C, With Husks Removed	0.1 ppm	0.1 ppm	Corn, Sweet, K+C, Husks Removed
Corn, Stover			Corn, Stover
Corn, Forage	1.0 ppm	1.0 ppm	Corn, Forage
		0.2 ppm	Corn, Milled Byproducts

Commodity	Established/Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Sorghum, Grain	1.0 ppm	1.0 ppm	Sorghum, Grain, Grain
Sorghum, Forage	0.1 ppm	0.1 ppm	Sorghum, Grain, Forage
Sorghum, Grain, Stover	0.1 ppm	0.1 ppm	Sorghum, Grain, Stover
Wheat, Grain	0.5 ppm	0.5 ppm	Wheat, Grain
Wheat, Forage	0.1 ppm	2.0 ppm	Wheat, Forage
Wheat, Straw	0.5 ppm	6.0 ppm	Wheat, Straw
		3.0 ppm	Wheat, Bran
		2.0 ppm	Wheat, Milled Byproducts
Cattle Fat,	0.5 ppm	Remove Tolerance	
Cattle, Meat	0.5 ppm	Remove Tolerance	
Cattle, Meat Byproducts	0.5 ppm	Remove Tolerance	
Goat, Fat	0.05 ppm	Remove Tolerance	
Goat, Meat	0.05 ppm	Remove Tolerance	
Goat, Meat Byproducts	0.05 ppm	Remove Tolerance	
Sheep, Fat	0.05 ppm	Remove Tolerance	
Sheep, Meat	0.05 ppm	Remove Tolerance	
Sheep, Meat Byproducts	0.05 ppm	Remove Tolerance	
Horse Meat	0.05 ppm	Remove Tolerance	
Hog, Fat	0.05 ppm	Remove Tolerance	
Hog, Meat	0.05 ppm	Remove Tolerance	
Hog, Meat Byproducts	0.05 ppm	Remove Tolerance	
Poultry, Fat	0.05 ppm	Remove Tolerance	
Poultry, Meat	0.05 ppm	Remove Tolerance	
Poultry, Meat Byproducts	0.05 ppm	Remove Tolerance	

SignOff Date:
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Branch: RRB3

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