SUMMARY

(In accordance with 40 CFR part 152, this summary is available for public release after registration)

STUDY TITLE

Dow AgroSciences' Response to the U.S. EPA Office of Pesticide Programs' (OPP) Notice for Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" for the Nitrapyrin Reregistration Eligibility Decision (RED) and Tolerance Reassessments

DATA REQUIREMENTS

None

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STUDY COMPLETED ON

December 17, 2004

PERFORMING LABORATORY

Regulatory Laboratories - Indianapolis Lab
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LABORATORY STUDY ID

MDC121704-1

Dow AgroSciences' Response to the U.S. EPA Office of Pesticide Programs' (OPP) Notice for Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" for the Nitrapyrin Reregistration Eligibility Decision (RED) and Tolerance Reassessments

SUMMARY

As requested by the EPA, Dow AgroSciences (DAS) is providing comments on the Agency's human health and environmental fate and effects risk assessments and related materials for nitrapyrin. These comments are intended to address errors and inconsistencies found in the EPA documents listed in Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" and the attachments included therein entitled:

OPP-2004-0283-0001: Nitrapyrin; Availablilty of Risk Assessments. Federal Register/ Vol. 69, No. 212/ Wednesday, November 3, 2004/ Notices

OPP-2004-0283-0002: Overview of Nitrapyrin Risk Assessment. October 6, 2004

OPP-2004-0283-0003: Dow AgroSciences' Response to the USEPA/OPP Preliminary Human Health and Environmental Fate and Effects Risk Assessment and Related Materials for the Nitrification Inhibitor Nitrapyrin Reregistraion Eligibility Document (RED). August 27, 2004

OPP-2004-0283-0004: Response to Comments from The Dow AgroSciences on Nitrapyrin Risk Assessment. PC Code: 069203, DP Barcode: D298451. September 30, 2004

OPP-2004-0283-0005: Nitrapyrin: Team Review of Metabolism Information. PC Code: 069203, DP Barcode: 299923. February 23, 2004

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OPP-2004-0283-0007: Environmental Fate and Effects Division Revised Risk Assessment for the Nitrapyrin Reregistration Eligibility Decision. PC Code: 069203, DP Barcode: D298448. October 7, 2004
[NOTE: Memorandum, Drinking Water Assessment for Nitrapyrin and It's Major Degradate 6-Chloropicolinic Acid (6-CPA). PC Code: 069203, DP Barcode: 299121. April 14, 2004, is included as Appendix B of this document, rather than as a separate document as reviewed in the 30-day "errors only" correction correspondence.]

OPP-2004-0283-0008: Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Nitrapyrin. PC Code: 069203, DP Barcode: D308334. September 30, 2004

OPP-2004-0283-0009: Nitrapyrin. Reregistration Action. Corrected Summary of Analytical Chemistry and Residue Data. PC Code: 069203, DP Number: D308740. September 29, 2004

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OPP-2004-0283-0012: Reviews of a number of studies submitted in support of the reregistration of nitrapyrin. DP Barcode: D207458. May 25, 2004

OPP-2004-0283-0013: Nitrapyrin Chronic Dietary Exposure Assessment for the Reregistration Eligibility Decision. PC Code: 069203, DP Barcode: D299299. May 14, 2004

OPP-2004-0283-0014: Nitrapyrin – 1st Report for the Hazard Identification Assessment Review Committee. PC Code: 069203, TXR No. 0052387. March 1, 2004

OPP-2004-0283-0015: Nitrapyrin: Team Review of Metabolism Information. PC Code: 069203, DP Barcode: 299923. February 23, 2004

OPP-2004-0283-0016: Nitrapyrin RED – Reregistration Eligibility Decision: Product Chemistry Considerations. PC Code: 069203, DP Barcode: D295601. February 19, 2004

OPP-2004-0283-0017: Memorandum; Nitrapyrin Use Closure Memo. June 27, 2004

OPP-2004-0283-0018: Nitrapyrin. Revised HED Chapter of the Registration Eligibility Decision Document (RED). PC Code: 069203, DP Barcode D298451. September 30, 2004

Dow AgroSciences appreciates the opportunity to provide comment on the EPA human health and environmental fate and effects risk assessments and related materials during the 60-day public comment period for the reregistration process of nitrapyrin. In the comments provided, DAS has highlighted several areas within the human health and environmental fate and effects risk assessments where errors and miscalculations are evident, where it is believed that potential risks are significantly overstated, where it is believed that unrealistic assumptions have been made, or where relevant information has been omitted. In general, comments raised are focused in the following areas: 1). Issues associated with dermal absorption values, and appropriate animal models for evaluating dermal absorption; 2). Assumptions regarding vapor pressure and volatility of nitrapyrin; 3). Assessment and use of relevant data in determining carcinogenic potential of nitrapyrin; and 4). Availability of support information (data) to clarify assessments of toxicity to aquatic plants and terrestrial organisms.

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DATA REQUIREMENTS

None

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STUDY COMPLETED ON

December 17, 2004

PERFORMING LABORATORY

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9330 Zionsville Road
Indianapolis, Indiana 46268-1054

LABORATORY STUDY ID

MDC121704-1

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

Compound: Nitrapyrin

Title: Dow AgroSciences' Response to the U.S. EPA Office of Pesticide Programs' (OPP) Notice for Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" for the Nitrapyrin Reregistration Eligibility Decision (RED) and Tolerance Reassessments

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10 (d)(1)(A)(B), or (C).*

Company: Dow AgroSciences LLC

Company Agent: Michael D. Culy

Title: Regulatory Manager

Signature: _____

Date: December 17, 2004

*In the United States, the above statement supersedes all other statements of confidentiality that may occur elsewhere in this report.

THIS DATA MAY BE CONSIDERED CONFIDENTIAL IN COUNTRIES OUTSIDE THE UNITED STATES.

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Title: Dow AgroSciences' Response to the U.S. EPA Office of Pesticide Programs' (OPP) Notice for Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" for the Nitrapyrin Reregistration Eligibility Decision (RED) and Tolerance Reassessments

Study Initiation Date: November 3, 2004 Study Completion Date: December 17, 2004
Experimental Start Date: N/A Experiment Termination Date: N/A

This report represents data generated after the effective date of the EPA FIFRA Good Laboratory Practice Standards.

United States Environmental Protection Agency
Title 40 Code of Federal Regulations Part 160
FEDERAL REGISTER, August 17, 1989

Organisation for Economic Co-Operation and Development
ISBN 92-64-12367-9, Paris 1982

This study does not meet requirements of 40 CFR Part 160.

	December 17, 2004
Michael D. Culy Sponsor Dow AgroSciences LLC	Date
	December 17, 2004
Michael D. Culy Submitter Dow AgroSciences LLC	Date
	December 17, 2004
Michael D. Culy Author Dow AgroSciences LLC	Date

QUALITY ASSURANCE STATEMENT

Compound: Nitrapyrin

Title: Dow AgroSciences' Response to the U.S. EPA Office of Pesticide Programs' (OPP) Notice for Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" for the Nitrapyrin Reregistration Eligibility Decision (RED) and Tolerance Reassessments

Study Initiation Date: November 3, 2004 Study Completion Date: December 17, 2004

NON-GLP STUDY

XVIII. DOW AGROSCIENCES' RESPONSE TO THE U.S. EPA OFFICE OF PESTICIDE PROGRAM'S (OPP) NOTICE FOR DOCKET ID: OPP-2004-0283, ENTITLED "NITRAPYRIN; AVAILABILITY OF RISK ASSESSMENTS" FOR THE NITRAPYRIN REREGISTRATION ELIGIBILITY DECISION (RED) AND TOLERANCE REASSESSMENTS

ABSTRACT

Dow AgroSciences (DAS) is providing comments on the Agency's human health and environmental fate and effects risk assessments and related materials for the nitrification inhibitor nitrapyrin as posted for 60-day public comment in EPA documents (Docket ID: OPP-2004-0283), entitled "Nitrapyrin; Availability of Risk Assessments". These comments will address errors and inconsistencies found in the EPA documents and the attachments included therein (comprehensive list of documents provided in the introduction).

Dow AgroSciences appreciates the opportunity to review and comment on the EPA human health and environmental fate and effects risk assessments and related materials during the 60-day public comment period for the reregistration process of nitrapyrin. In the comments provided, DAS has highlighted several areas within the human health and environmental fate and effects risk assessments where errors and miscalculations are evident, where it is believed that potential risks are significantly overstated, where it is believed that unrealistic assumptions have been made, or where relevant information has been omitted. In these comments, DAS discusses areas where improvements in the risk assessment process could occur through alternate interpretations in methodology and correction of specific errors. In general, DAS agrees with the assessments that EFED have conducted for the human health and environmental fate and effects studies available for nitrapyrin. However, DAS has identified a few areas of concern where comments are provided. The comments raised are focused in the following areas: 1). Issues associated with dermal absorption values, and appropriate animal models for evaluating dermal absorption; 2). Assumptions regarding vapor pressure and volatility of nitrapyrin; 3). Assessment and use of relevant data in determining carcinogenic potential of nitrapyrin; and 4).

Availability of support information (data) to clarify assessments of toxicity to aquatic plants and terrestrial organisms.

INTRODUCTION

Dow AgroSciences (DAS) is providing comments on the Agency's human health and environmental fate and effects risk assessments and related materials for nitrapyrin. These comments will address errors and inconsistencies found in the EPA documents listed in Docket ID: OPP-2004-0283, entitled "Nitrapyrin; Availability of Risk Assessments" and the attachments included therein entitled:

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Dow AgroSciences appreciates the opportunity to provide comment on the EPA human health and environmental fate and effects risk assessments and related materials during the 60-day public comment period for the reregistration process of nitrapyrin. In the comments provided, DAS has highlighted several areas within the human health and environmental fate and effects risk assessments where errors and miscalculations are evident, where it is believed that potential risks are significantly overstated, where it is believed that unrealistic assumptions have been made, or where relevant information has been omitted. In these comments, DAS discusses areas where improvements in the risk assessment process could occur through alternate interpretations in methodology and correction of specific errors.

GENERAL COMMENTS

DAS has identified four primary areas of concern in the documents and has provided specific comments. In general, these areas of concern are focused on the following:

1) The text in several documents repeatedly states that the dermal absorption value for nitrapyrin is 46%. This is an erroneous statement, based on an error in the HIARC report (page 10) for nitrapyrin (dated March 1, 2004) whereby the 46% value represents the mean absorption (34.61%) plus the standard deviation (10.64%). This large standard deviation is primarily due to a low value of 19.30% for one animal and reflects significantly lower absorption than other animals. This would indicate that adding the standard deviation to the

mean absorption value is not justified. The HED Chapter (and other references) should reflect the actual dermal absorption study results of **34.61±10.64%** at **72 hr** post-dosing.

The text in the HED Chapter mentions repeatedly that "the rabbit is a poor model for assessing dermal toxicity" to nitrapyrin. DAS feels that this determination is incorrect. The results of the Nitrapyrin 21-day repeated dose dermal toxicity study in rabbits (Cosse et al., 1992: MRID 42239301) **demonstrate target organ effects in the liver that are consistent with the findings following oral exposures in mice, rats, rabbits and dogs.** The study results indicate statistically significant increases in absolute and relative liver weights in rabbits following 21 days of dermal treatment with 1000 mg Nitrapyrin/kg/day. **The increased liver weights following dermal exposure to rabbits contradict a conclusion that "…the rabbit is a poor model for assessing dermal toxicity**."

2) Assumptions regarding vapor pressure and volatility of nitrapyrin. DAS is pleased that the Agency's Environmental Fate and Effects Division agrees that nitrapyrin is not highly volatile, and has indicated in document OPP-2004-0283-0006 that all references to "highly volatile will be changed to "volatile". However, DAS still believes there is too much focus on volatility. Atmospheric transfer is not expected to be an important route of dissipation for nitrapyrin, as most applications are made by soil injection. The EPI Suite Fugacity Model estimates the global steady-state concentrations of a material in generalized air, soil, water and sediment compartments. When soil-incorporated emissions to soil are the modeled route of release into the environment, EPI Suite Fugacity Model estimates at steady-state that only 0.0608% of the soil emissions would transfer to the air."

3). Assessment and use of relevant data in determining carcinogenic potential of nitrapyrin. Dow AgroSciences takes exception to the statement "Nitrapyrin is classified as 'likely to be a human carcinogen' based on the mouse study which demonstrated liver tumors, stomach tumors and Hardarian gland neoplasms." The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC

report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were

decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency. This scientific review has been submitted during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process of nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

4) Availability of support information (data) to clarify assessments of toxicity to aquatic plants and terrestrial organisms. The EFED Chapters have concluded that nitrapyrin data were not

available for quantitative risk assessments of aquatic plant toxicity. As a result, toxicity of nitrapyrin to green algae was estimated (based on calculations) in the documents. Dow AgroSciences does have a study evaluating toxicity of nitrapyrin to Selenastrum capricornutum algae that can be utilized to revise these conclusions. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences has submitted this additional study, "Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

The EFED Chapters have also concluded that nitrapyrin data were not available for quantitative risk assessment of soil organisms. As a result, toxicity of nitrapyrin to soil organisms (earthworms) was assumed to be potentially "significant", based on calculated concentrations in the soil. Because EFED 'currently does not quantify risks to terrestrial non-target insects', EFED has contradicted itself in suggesting that toxicity information for earthworms should be submitted to 'quantify these risks." The EFED statement in Document Detail OPP-2004-0283-0007, Environmental Fate and Effects Division Revised Risk Assessment for Nitrapyrin Reregistration Eligibility Decision, page 122, third paragraph, states that "Currently, EFED does not perform assessments for chronic risk to plants, acute or chronic risks to non-target insects, or chronic risk from granular/bait formulations to mammalian or avian species", and is clear in this regard. Submission of such tests should therefore not be required. Nonetheless, Dow AgroSciences does have a study evaluating toxicity of nitrapyrin to earthworms. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences has submitted an additional study, "Nitrapyrin: Determination of the Toxicity to the Earthworm *(Eisenia foetida)*", MRID No. 46411402, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported a 15 day LC50 = 209 mg ai/kg soil and a EEC in soil (2.7 mg ai/kg dry wt soil) which is well below the 15 day LC50, and hence, a low risk to earthworms.

SPECIFIC COMMENTS: U.S. EPA OFFICE OF PESTICIDE PROGRAM'S (OPP) NOTICE FOR DOCKET ID: OPP-2004-0283, ENTITLED "NITRAPYRIN; AVAILABILITY OF RISK ASSESSMENTS" FOR THE NITRAPYRIN REREGISTRATION ELIGIBILITY DECISION (RED) AND TOLERANCE REASSESSMENTS

I. OPP-2004-0283-0001: Nitrapyrin; Availablilty of Risk Assessments. Federal Register/ Vol. 69, No. 212/ Wednesday, November 3, 2004/ Notices

This is the posted Federal Register notice. Dow AgroSciences has no corrections or comments on this document.

II. OPP-2004-0283-0002: Overview of Nitrapyrin Risk Assessment. October 6, 2004

Page 4, Table 1, third line, Cancer (oral, dermal, inhalation) The statement "Classified as "likely to be a carcinogen in humans" as per May 5, 2000 CARC report" **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a

mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

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In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

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conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

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Page 7, Table 2, second line, Sprays for Groundboom Application (2): The value for "Total PPE1 Short-Term MOE" of "410" is incorrect, based on Document No OPP-2004-0283-0008, Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Nitrapyrin, where it is stated as "420" (Table 5). **The value should be changed to "420".**

Page 8, Table 3, second note under table:. The statement, "PPE1 cancer risk includes long pants, long shirts, double layer and no respirator", incorrectly lists "double layer". The term "double layer" should be deleted.

Page 9, second paragraph, lines 2 to 3: The statement, "It is mobile to moderately mobile in mineral soils, and prone to volatilize from the application site….", is overstated. Based on comments provided for the EFED chapter (OPP-2004-0283-0007), it is recommended that the statement read "may have potential to volatilize".

Page 10, Status of Data: DAS does not agree with the list of required studies identified as "Data Gaps". Several studies have been provided to the Agency as a result of requests made during the 60-day comment period, and it is believed that these studies, along with several older reports that examine degradation of 6-CPA under various temperature, moisture and soil conditions, will satisfy the requirements for some of these proposed studies. Current modeling information and inherent levels of risk for nitrapyrin and 6-CPA as discussed in the EFED, HED, Toxicology, and Hazard Identification Assessment science chapters would suggest that these studies may not be necessary.

III. OPP-2004-0283-0003: Dow AgroSciences' Response to the USEPA/OPP Preliminary Human Health and Environmental Fate and Effects Risk Assessment and Related Materials for the Nitrification Inhibitor Nitrapyrin Reregistraion Eligibility Document (RED). August 27, 2004

Dow AgroSciences has no corrections or comments on this document.

IV. OPP-2004-0283-0004: Response to Comments from The Dow AgroSciences on Nitrapyrin Risk Assessment. PC Code: 069203, DP Barcode: D298451. September 30, 2004

Dow AgroSciences may not agree with all Agency responses provided in this document. Specific corrections or comments from DAS will be provided in review of the individual science chapter documents listed in documents within OPP-2004-0283.

V. OPP-2004-0283-0005. Nitrapyrin: Team Review of Metabolism Information. PC Code: 069203, DP Barcode: 299923. February 23, 2004

3. BRIEFING MATERIALS
RESIDUE CHEMISTRY
Toxicology

Page 13, third line of Table 3.12. Toxicological Endpoints: The statement "Classified as "likely to be a carcinogen in humans" as per May 5, 2000 CARC report. Q1* = 4.25 x 10-2 human equivalents (refer to TXR #0014035, memo dated 3/9/00**" is believed to be incorrect**.

Response: As indicated above, the Scientific Advisory Group (Hardisty, 2004) concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

VI. OPP-2004-0283-0006. Environmental Fate and Effects Division Response to Error Correction Comments made by Dow AgroSciences (letter dated 27 August 2004) for

the Preliminary Risk Assessment on Nitrapyrin. PC Code: 069203, DP Barcode: D298448. October 7, 2004

Dow AgroSciences may not agree with all Agency responses provided in this document. Specific corrections or comments from DAS will be provided in review of the complete document, OPP-2004-0283-0007.

VII. OPP-2004-0283-0007. Environmental Fate and Effects Division Revised Risk Assessment for the Nitrapyrin Reregistration Eligibility Decision. PC Code: 069203, DP Barcode: D298448. October 7, 2004

MEMORANDUM

Page 4, first bullet point: The statement "Label revisions requiring that soil incorporation occur immediately after application…" provides for a mechanical incorporation procedure that is not practical to implement in a farming situation. Incorporation activities must be employed with a reasonable time period for completion, as tillage equipment is typically utilized as part of an additional field operation; thereby not effectively "immediate" in most cases.

Page 5, Suggested Label Language, End Use Products, line 4 to 5: The statement "Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas" is not needed. The aquatic risk assessment for nitrapyrin demonstrates very low Risk Quotients and indicates that this statement is not needed. USEPA agreed in the Error-Only comment response and removed only one of the two instances in which this sentence appeared in this paragraph.

SCIENCE CHAPTER: Environmental Fate and Effects Division's Revised Risk Assessment for the Reregistration Eligibility Decision for Nitrapyrin

Environmental Risk Conclusions

Environmental Risk Summary

Page 2, third paragraph, lines 4 to 5: The statement "No predicted or measured toxicity information is available regarding other classes of aquatic plants." can be revised based on additional information. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

Introduction

Physical and Chemical Properties of Nitrapyrin and 6-Chloropicolinic Acid

Page 4, K_d value: The term "***0.8 ml/g***" for the K_d value is not a calculation provided by the "EPI Suite". Rather, the module PCKOCWIN only provides an estimate for K_{oc}. The K_{oc} estimate from EPI Suite for nitrapyrin is 23.5 ml/g. It would appear that EFED has applied a soil organic carbon fraction to the K_{oc} estimate to arrive at this K_d value. EFED should indicate the calculation that it made to derive K_d and also provide the K_{oc} estimate that they derived from the EPI Suite in this listing.

Risk Assessment Approach

Measures of Effects

Page 11, bullet 2, sub-bullet 1, Algae and aquatic plants: The statement "No data were available, , toxicity of nitrapyrin to green algae was estimated using ECOSAR (v0.99g, http://www.epa.gov/oppt/newchems/21ecosar.htm)." can be revised based on additional information. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004

(accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

Measures of Exposure

Terrestrial Animals

***Page 13, fourth paragraph, lines 1 to 3*:** The statement "Because nitrapyrin is a **volatile compound**, the potential for inhalation of vapor phase nitrapyrin by terrestrial wildlife was identified as a potential exposure route not quantitatively addressed by existing RQ calculation exposure methods."

Response: DAS is pleased that the Agency's Environmental Fate and Effects Division agrees that nitrapyrin is not highly volatile, and has indicated in document OPP-2004-0283-0006 that all references to "highly volatile will be changed to "volatile". However, DAS still believes there is too much focus on volatility. Atmospheric transfer is not expected to be an important route of dissipation for nitrapyrin, as most applications are made by soil injection. The EPI Suite Fugacity Model estimates the global steady-state concentrations of a material in generalized air, soil, water and sediment compartments. When soil-incorporated emissions to soil are the modeled route of release into the environment, EPI Suite Fugacity Model estimates at steady-state that only 0.0608% of the soil emissions would transfer to the air.

Integrated Environmental Risk Characterization

Risks to Aquatic Organisms

Page 15, fourth paragraph, lines 1 to 3: The statement "Aquatic plant toxicity data were not available for nitrapyrin; therefore, a quantitative risk assessment involving calculation of RQs was not conducted. However, toxicity of nitrapyrin to green algae was estimated using ECOSAR (v0.99g, http://www.epa.gov/oppt/newchems/21ecosar.htm)." can be revised based on additional information. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study,

"Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

Risks to Terrestrial Non-Target Insects

Page 15, fifth paragraph, lines 3 to 5: The statement "However, nitrapyrin exposure to beneficial ground dwelling insects and other beneficial organisms may be significant, and no toxicity information is available for these organisms in order to quantify these risks"…. **is incorrect, based on available data**.

Response: Because EFED 'currently does not quantify risks to terrestrial non-target insects', EFED has contradicted itself in suggesting that toxicity information for earthworms should be submitted to 'quantify these risks." The EFED statement in this document (page 122, third paragraph), "Currently, EFED does not perform assessments for chronic risk to plants, acute or chronic risks to non-target insects, or chronic risk from granular/bait formulations to mammalian or avian species." is clear in this regard. Submission of such tests should therefore not be required. Nonetheless, Dow AgroSciences does have a study evaluating toxicity of nitrapyrin to earthworms. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Determination of the Toxicity to the Earthworm *(Eisenia foetida)*", MRID No. 46411402, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported a 15 day LC50 = 209 mg ai/kg soil and a EEC in soil (2.7 mg ai/kg dry wt soil) which is well below the 15 day LC50, and hence, a low risk to earthworms.

Environmental Fate Assessment

Page 17, third paragraph, lines 7 to 8: The statement "Nitrapyrin also has a **high vapor pressure** (2.8 e-3 torr) and hence is **prone to volatilization** from the application site."

Response: DAS is pleased that the Agency's Environmental Fate and Effects Division agrees that nitrapyrin is not highly volatile, and has indicated in document OPP-2004-0283-0006 that all references to "highly volatile will be changed to "volatile". However, DAS still believes there is too much focus on volatility. Atmospheric transfer is not expected to be an important route of dissipation for nitrapyrin, as most applications are made by soil injection. The EPI Suite Fugacity Model estimates the global steady-state concentrations of a material in generalized air, soil, water and sediment compartments. When soil-incorporated emissions to soil are the modeled route of release into the environment, EPI Suite Fugacity Model estimates at steady-state that only 0.0608% of the soil emissions would transfer to the air.

Aquatic Hazard, Exposure, and Risk Assessment

Hazard Summary

Toxicity to Aquatic Plants

Page 19, third paragraph, line 1: The statement "No aquatic plant data were submitted to the Agency." can be refined based on additional information. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

Reported Aquatic Incidences

Page 19, fourth paragraph, lines 2 to 6: The statement "The lack of reported incidents cannot be considered as evidence of lack of hazard. Incident reporting is a voluntary process. No attempt has been made to actively investigate if mortality of aquatic species is occurring near fields treated with nitrapyrin. At the present time, the lack of mortality incidents in the Ecological Incident Information System (EIIS) database cannot be considered as evidence of a lack of hazard to aquatic organisms." **is inaccurate and misleading**.

Response: When coupled with the moderately toxic classification of acute toxicity to fish and aquatic invertebrates, it is reasonable to infer that the lack of reported incidents is consistent with the minimal aquatic risk associated with the use of nitrapyrin. The conservative risk assessment presented by EFED is further evidence of the minimal aquatic risk of this product. EFED has often concluded for other products that EIIS reports of mortality are evidence of risk. To conclude that EIIS information is completely uninformative about the converse situation (i.e. minimal risk) appears to be a double standard in interpretation of the Agency's own data and risk assessment. **The paragraph should end after the sentence, "No aquatic incidents have been reported to the Agency for nitrapyrin as of December 1, 2003."**

Risk Quotients

Aquatic Plants

Page 22, fifth paragraph, line 1: The statement "No aquatic plant data were submitted to the Agency; therefore, RQs cannot be determined." can be revised based on additional information. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

Aquatic Organism Risk Characterization

Risks to Aquatic Plants

Page 23, third paragraph, lines 1 to 3: The statement "Aquatic plant toxicity data were not available for nitrapyrin; therefore, a quantitative risk assessment could not be conducted. However, toxicity of nitrapyrin to green algae can be estimated using ECOSAR (v0.99g, http://www.epa.gov/oppt/newchems/21ecosar.htm)." can be revised based on additional information. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Toxicity to Green Alga *(Selenastrum capricornutum)*", MRID No. 46411401, on November 19, 2004

(accepted by the Agency on November 23, 2004). In summary, this study reported an EC_{50} based on growth rate of 1.7 mg/L and based on biomass of 0.92 mg/L.

Uncertainties in the Aquatic Assessment

Page 25, uncertainty no. 5, lines 1 to 4: The statement "Volatilization, transport and deposition of nitrapyrin are not addressed quantitatively as a route of exposure for aquatic organisms. Based on the physical chemical properties of nitrapyrin there may be a concern for impacts to non-target organisms for the delayed soil incorporated applications **due to volatilization** and off-site deposition of nitrapyrin."

Response: DAS is pleased that the Agency's Environmental Fate and Effects Division agrees that nitrapyrin is not highly volatile, and has indicated in document OPP-2004-0283-0006 that all references to "highly volatile will be changed to "volatile". However, DAS still believes there is too much focus on volatility. Atmospheric transfer is not expected to be an important route of dissipation for nitrapyrin, as most applications are made by soil injection. The EPI Suite Fugacity Model estimates the global steady-state concentrations of a material in generalized air, soil, water and sediment compartments. When soil-incorporated emissions to soil are the modeled route of release into the environment, EPI Suite Fugacity Model estimates at steady-state that only 0.0608% of the soil emissions would transfer to the air.

Hazard Summary

Toxicity to Birds

Page 26, second paragraph, lines 4 to 6: The statement "A non-definitive LD_{50} of >2510 mg/kg-bwt was obtained in the core study using mallard ducks, and toxic symptoms (lethargy, loss of coordination, lower limb weakness) were noted in all dose groups receiving >631 mg/kg-bwt." **requires clarification**.

Response: The study result is definitive in the sense that it defines the LD_{50} as greater than 2510 mg/kg-bwt. The characterization of the result of this core guideline study as

'*non-definitive*' is unnecessarily pejorative. A more objective description of the study results would simply state, "***An LD_{50} of >2510 mg/kg-bwt (the highest dose tested) was obtained in the core study … .***"

Page 26, fourth paragraph, lines 2 to 3: The statement "Non-definitive LC_{50}'s of >4640 and>5000 mg ai/kg-diet were attained for mallard ducks and Japanese quail, respectively (Acc. 117106 and 116899)." **requires clarification**.

Response: The study results are definitive in the sense that they define the dietary LC_{50} as greater than the highest concentration tested. The characterization of the results of these studies as '*non-definitive*' is unnecessarily pejorative. A more objective description of the study results would simply state, ***"LC_{50}'s of >4640 and >5000 mg ai/kg-diet (the highest concentrations tested) were obtained for mallard ducks and Japanese quail, respectively (Acc. 117106 and 116899)."***

Toxicity to Terrestrial Plants

Page 28, third paragraph, lines 10 to 12: The statement "…but this study does provide anecdotal evidence that nitrapyrin is less phytotoxic than several of the commercial herbicides available in 1968." **should be deleted**. Even though the study was non-guideline, the study results should not be described condescendingly as 'anecdotal.' **The statement serves no purpose**.

Terrestrial Organism Risk Characterization

Risks to Birds and Mammals

Exposure routes other than dietary

Page 35, third paragraph, line 1: "Because nitrapyrin is **highly volatile** (v.p. $2.8x10^{-3}$ torr) inhalation of gas phase nitrapyrin may be a significant contributor to overall exposure."

Response: The term "highly volatile" should be changed to "volatile". DAS is pleased that the Agency's Environmental Fate and Effects Division agrees that nitrapyrin is not highly volatile, and has indicated in document OPP-2004-0283-0006 that all references to "highly volatile will be changed to "volatile". However, DAS still believes there is too much focus on volatility. Atmospheric transfer is not expected to be an important route of dissipation for nitrapyrin, as most applications are made by soil injection. The EPI Suite Fugacity Model estimates the global steady-state concentrations of a material in generalized air, soil, water and sediment compartments. When soil-incorporated emissions to soil are the modeled route of release into the environment, EPI Suite Fugacity Model estimates at steady-state that only 0.0608% of the soil emissions would transfer to the air.

Page 37, first paragraph, lines 3 to 5: The statement "However, nitrapyrin exposure to beneficial ground dwelling insects and other beneficial organisms may be significant, and no toxicity information is available for these organisms in order to quantify these risks"…. **is incorrect, based on available data**.

Response: Because EFED 'currently does not quantify risks to terrestrial non-target insects', EFED has contradicted itself in suggesting that toxicity information for earthworms should be submitted to 'quantify these risks." The EFED statement in this document (page 122, third paragraph), "Currently, EFED does not perform assessments for chronic risk to plants, acute or chronic risks to non-target insects, or chronic risk from granular/bait formulations to mammalian or avian species." is clear in this regard. Submission of such tests should therefore not be required. Nonetheless, Dow AgroSciences does have a study evaluating toxicity of nitrapyrin to earthworms. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Determination

of the Toxicity to the Earthworm *(Eisenia foetida)*", MRID No. 46411402, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported a 15 day LC50 = 209 mg ai/kg soil and a EEC in soil (2.7 mg ai/kg dry wt soil) which is well below the 15 day LC50, and hence, a low risk to earthworms.

Page 38, second paragraph, lines 1 to 8: The statement reads "**The effects of nitrapyrin on beneficial soil organisms are unknown**. EFED concluded that the potential risks to honey bees from nitrapyrin would be low since expected exposure would be very low. However, the exposure of nitrapyrin to soil organisms may be significant. Assuming an application rate of 0.9 lbs ai/acre and a 4" incorporation depth, the soil concentration of nitrapyrin is estimated to be 2.7 mg ai/kg-dry wt soil. It is unknown at what concentrations nitrapyrin may have toxic effects on these beneficial soil organisms (e.g., earthworms). To reduce this uncertainty, **EFED suggests that the registrant submit an earthworm toxicity test for nitrapyrin to the Agency**."

Response: Because EFED 'currently does not quantify risks to terrestrial non-target insects', EFED contradicts itself in suggesting that toxicity information for earthworms should be submitted to 'quantify these risks." The EFED statement in this document (page 122, third paragraph), "Currently, EFED does not perform assessments for chronic risk to plants, acute or chronic risks to non-target insects, or chronic risk from granular/bait formulations to mammalian or avian species." is clear in this regard. Submission of such tests should therefore not be required. Nonetheless, Dow AgroSciences does have a study evaluating toxicity of nitrapyrin to earthworms. Based on a November 8, 2004 request from Stephanie Plummer, EPA Chemical Review Manager, Dow AgroSciences submitted an additional study, "Nitrapyrin: Determination of the Toxicity to the Earthworm *(Eisenia foetida)*", MRID No. 46411402, on November 19, 2004 (accepted by the Agency on November 23, 2004). In summary, this study reported a 15 day LC50 = 209 mg ai/kg soil and a EEC in soil (2.7 mg ai/kg dry wt soil) which is well below the 15 day LC50, and hence, a low risk to earthworms.

Memorandum: Drinking Water Assessment for Nitrapyrin and its Major Degradate 6-Chloropicolinic Acid (6-CPA)

A- Surface Water

Page 47, fourth paragraph, lines 3 to 8: The statement "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." **is too conservative.**

Response: 6-chloropicolinic acid (6-CPA) degradation rates were assumed to be between 365 days and 10,000 days in PRZM/EXAMS and SciGrow modeling (refer to page 7 of the Drinking Water Assessment, DP Barcode: 299121). DAS believes this approach to be too conservative. The 6-CPA aerobic metabolism rate, at maximum expected soil concentrations, will be less than 365 days. **EECs generated with the 365-d half-life should be considered the upper estimate for risk assessment** purposes. Further, a modeling assumption is that 100% of the applied nitrapyrin is converted to 6-CPA immediately. **This should be identified as a worst-case assumption**.

The Agency did not take into account data already submitted by the registrant with regard to the persistence of 6-CPA. MRID#00117010 contains 6-CPA results from an accepted aerobic soil study of nitrapyrin. DAS, for this response, calculated decline rates for 6-CPA from its peak. The resultant first-order half life ranged from about 77 d to 330 d in two soils. In addition the following list of previously submitted documents provide supplemental information on the degradation of 6-CPA.

Study Title	Author	Date Submitted	MRID
Factors Influencing the Decomposition of 6-Chloropicolinic Acid in Soil	Youngson, C. R., et. al.	4/21/1972	00116913
The Decomposition of 6-Chloropicolinic Acid in Soil: Effect of Temperature	Meikle, R. W., et al.	4/21/1972	00116914
The Decomposition of 6-Chloropicolinic Acid in Soil: Effect of Soil Sterilization	Meikle, R. W., et al.	4/21/1972	00116915
Are Soil Microorganisms the Chief Source of Decomposition of 6-Chloropicolinic Acid in Soil?	Youngson, C. R.	4/21/1972	00116916

C- Uncertainties, Limitations, and Restrictions

Page 54, uncertainty no. 1, lines 1 to 2 and 5 to 6: The statements "Nitrapyrin is **a volatile compound** with a vapor pressure of 2.8 e-3 mm Hg and a Henry's constant of 2.13 e-5 atm m^3/mol…." and "**Atmospheric transfer is expected** to be a potential route of dissipation for nitrapyrin."

Response: DAS is pleased that the Agency's Environmental Fate and Effects Division agrees that nitrapyrin is not highly volatile, and has indicated in document OPP-2004-0283-0006 that all references to "highly volatile will be changed to "volatile". However, DAS still believes there is too much focus on volatility. Atmospheric transfer is not expected to be an important route of dissipation for nitrapyrin, as most applications are made by soil injection. The EPI Suite Fugacity Model estimates the global steady-state

concentrations of a material in generalized air, soil, water and sediment compartments. When soil-incorporated emissions to soil are the modeled route of release into the environment, EPI Suite Fugacity Model estimates at steady-state that only 0.0608% of the soil emissions would transfer to the air.

APPENDIX G: Detailed Risk Quotients

Page 132, Table G-6: The column heading for "acute RQ" under Predicted Mean residues, is incorrect. The heading should read "Chronic RQ".

VIII. OPP-2004-0283-0008 Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Nitrapyrin. PC Code: 069203, DP Barcode: D308334. September 30, 2004

EXECUTIVE SUMMARY

Hazard Concerns

Page 4, fourth paragraph: The statement "Nitrapyrin is classified as "likely to be a human carcinogen" based on the mouse study which demonstrated liver tumors, stomach tumors and Hardarian gland neoplasm. The Q1* was determined to be 4.25 x 10-2 (mg/kg/day)-1 human equivalents." **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor

mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD

policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

1.0 BACKGROUND

1.1 Summary of Toxicity Concerns Relating to Agricultural Exposures

Endpoints of Concern

Page 7, last line of Table 2: The statement "Classified as "likely to be a carcinogen in humans" **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ

toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003)

2.0 OCCUPATIONAL EXPOSURES

2.1 Handler Exposures & Assumptions

2.1.4 Calculation of Dose:

Page 12, First equation: *Is described as "Average Daily Dose", and should be described as* ***Average Daily Dermal Dose***

Page 12, Second equation: *Is described as "Average Daily Inhalation Dose" with the second half reading as "=daily exposure. The second half of this equation should be described as* ***"=daily inhalation exposure''.***

2.2 Risk from Handler Exposure

2.2.1 Summary of Handler MOEs and Cancer Risk

Page 15, paragraph 5, line 3. The discussion of PPE1 for Table 6 is defined incorrectly. It incorrectly lists "double layer" (and should not).

APPENDIX B

Page 26, Table B1: Footnote "a" includes the term "**Baseline**" which should read as "**Baseline**"

Page 27, Table B2: The term **"double layer" should be removed** from comments below the footnotes.

IX. OPP-2004-0283-0009. Nitrapyrin. Reregistration Action. Corrected Summary of Analytical Chemistry and Residue Data. PC Code: 069203, DP Number: D308740. September 29, 2004

Regulatory Recommendations and Residue Chemistry Deficiencies

Page 4, Table 1: The new proposed tolerances for wheat, corn, and sorghum are acceptable to Dow AgroSciences. Will the new tolerances be instated with issuance of the RED document, or will DAS be required to submit a proposed tolerance petition to initiate the changes?

X. OPP-2004-0283-0010. Review of Nitrapyrin Incident Reports. DP Barcode: D308757, Chemical #069203. September 29, 2004

At this time, Dow AgroSciences has no corrections or comments on this document.

XI. OPP-2004-0283-0011. Nitrapyrin: Revised Toxicology Chapter for the RED. PC Code: 069203, DP Barcode: DP298451, TXR #0052870. September 28, 2004

1.0 HAZARD CHARACTERIZATION

Page 6, paragraph 1: (Carcinogenicity): Dow AgroSciences takes exception to the statement "Nitrapyrin is classified as 'likely to be a human carcinogen' based on the mouse study which demonstrated liver tumors, stomach tumors and Hardarian gland neoplasms."

Response: The Agency has not included all relevant studies and information and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin (see response below for Section 4.6 Carcinogenicity). Specifically, the CARC report for Nitrapyrin (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID

41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. Furthermore, the changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003, and thus does not reflect the current scientific position of the Agency. In addition, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the Toxicology chapter position (4.7 Mutagenicity, page 17-18) that "Nitrapyrin is not considered to have a mutagenicity or genetic toxicity concern."

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that Nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded

the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according to the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

4.0 HAZARD ASSESSMENT
4.2 Subchronic Toxicity
870.3200 21/28-Day Dermal Toxicity – Rat [sic]

Page 10, paragraph 6: *Classification.* In line 2, the statement reads "Since the study assessed only 5 animals/sex/dose rather than the 10/sex/dose currently required by the 870.3200 guidelines the study does not satisfy the guideline requirement for a 21 day dermal toxicity study."

Response: Dow AgroSciences is pleased that reviewers consider the study as "ACCEPTABLE/Non-Guideline", but contends that it in fact does satisfy guideline requirements. The 870.3200 test guideline was published in August, 1998. The 21-day dermal toxicity study was reported in February, 1992. Treatment groups of 5 animals/sex/dose complied with the EPA guidelines at the time of the study (FIFRA 82-2, 1984) as well as OECD Test Guideline 410 (1981) which is still the current OECD guideline. The EPA has agreed to accept studies conducted according to OECD test guidelines.

4.5 Chronic Toxicity
870.4100a (870.4300) Chronic Toxicity – Rat

Page 14, paragraph 5, line 16: The statement "At Month 24, the liver surface appeared roughened upon gross examination in the females (11 treated vs 4 controls: n=50)."….. should read "….. **11 high dose vs 4 controls.**…"

4.6 Carcinogenicity

870.4200b Carcinogenicity (feeding) – Mouse

Page 16 and 17:

Response: **The reviewers have not included all relevant studies and information in this assessment.** The CARC report for Nitrapyrin (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. Furthermore, the changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003 and thus does not reflect the current scientific position of the Agency. In addition, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the Toxicology chapter position (4.7 Mutagenicity, page 18) that "Nitrapyrin is not considered to have a mutagenicity or genetic toxicity concern."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary

administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. None of these dose levels resulted in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that Nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according to the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

Page 16, Executive Summary paragraph 1, line 4-5: The reference for the special study on hepatocyte proliferation and apoptosis in mice, **MRID 44231801, is not included in the reference list for the chapter**. The citation is:

Yano, B. and L. McFadden (1996). Nitrapyrin (N-Serve* Nitrogen Stabilizer): Quantitation of hepatocyte proliferation and apoptosis in a 2-week dietary toxicity study in B6C3F1 mice – a retrospective study. The Dow Chemical Company, Toxicology Research Laboratory, Midland, MI 48674, Laboratory Project study ID K-031304-038, June 24, 1996. Unpublished.

Page 17, second paragraph, line 4: The reference to "A special 2-week study **(MRID 44231801) with higher doses…." is not included in the reference list for the chapter**. The citation is:

Yano, B. and L. McFadden (1996). Nitrapyrin (N-Serve* Nitrogen Stabilizer): Quantitation of hepatocyte proliferation and apoptosis in a 2-week dietary toxicity study in B6C3F1 mice – a retrospective study. The Dow Chemical Company, Toxicology Research Laboratory, Midland, MI 48674, Laboratory Project study ID K-031304-038, June 24, 1996. Unpublished.

4.9 Metabolism

870.7485 Metabolism – Rat

Page 19, paragraph 3: The reference to "In a metabolism study **(1987, MRID No.: 40305501)...." is not included in the reference list for the chapter**. The citation is:

Timchalk, C., Dryzga, M., and Campbell, R. (1987). The metabolism and tissue distribution of orally administered 14C-Nitrapyrin in Fischer 344 rats. The Dow Chemical Company, Toxicology Research Laboratory, Midland, MI 48674, Laboratory Project study ID K-031304-026. Unpublished report.

870.7485 Metabolism – Mouse

Page 19, paragraph 6, line 1: The reference to "In a metabolism study **(1998, MRID No.: 44679301)…." is not included in the reference list for the chapter**. The citation is:

Domoradzki, J. and Brzak, K. (1988). Nitrapyrin: Metabolism and tissue distribution of 14C-labeled nitrapyrin in B6C3F1 mice. The Dow Chemical Company, Toxicology Research Laboratory, Midland, MI 48674, Laboratory Project study ID 971119. Unpublished report.

5.0 TOXICITY ENDPOINT SELECTION
5.2 Dermal Absorption

Page 21, paragraph 5: The statement reads "Dermal Absorption Factor; 46% based upon the dermal absorption study (1997, MRID 44282501) in rats… Not [sic] upper limit of the dose absorbed after 72 hours was selected."

Response: The value of 46% is not correct based on the study report (Domoradzki and Gibson, 1997; MRID 44282501). The study report states that **24.58±6.43%** of the dose was absorbed at 24 hr following a single dermal **24 hr** exposure to Nitrapyrin (18% remained on the skin after washing at 24 hr and thus potentially was available for further absorption). At **72 hr** post-dosing, **34.61±10.64%** of the applied dose was absorbed (with 24.58% absorbed in the first 24 hr).

The HIARC report for Nitrapyrin (dated March 1, 2004) appears to be the source of the dermal absorption value of 46%. The HIARC report (page 10) states that:

> *"…it was demonstrated nitrapyrin has a potential to remain on the skin following washing and this residual chemical can be absorbed to result in 34.6%±being absorbed over time. This high value of 46% represents the mean (~35%) plus the standard deviation (11)."*

There is no statistical or scientific basis for adding the standard deviation to the mean absorption value.

Examination of Table 7 of the dermal absorption study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 4 animals tested at 72 hr post-dosing had dermal absorption values of: 42.38, 19.30, 35.48, and 41.27% resulting in a mean value of 34.61% and a standard deviation of 10.64%. Obviously, the relatively large standard deviation primarily is due to the low value of 19.30% for one animal and reflects significantly lower absorption than the other animals. Thus, in contrast to the HIRAC procedure of adding the standard deviation to the mean value to derive a dermal absorption value of ~46%, a more reasonable process would be to subtract the standard deviation from the mean value. However, the important point is that evaluation should reflect the actual dermal absorption study results of **34.61±10.64%** at **72 hr** post-dosing.

5.3 Classification of Carcinogenic Potential

Page 21, paragraph 6: The statement reads "As per the CARC report dated May 5, 2000, nitrapyrin is classified as "likely to be a carcinogen in humans" using the criteria in the Draft Guidelines for Carcinogen Risk Assessment (July, 1999)…." **and is believed to be incorrect.**

Response: As indicated above, the Scientific Advisory Group (Hardisty, 2004) concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

Appendix

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Page 30, first line in table, 870.4200 Carcinogenicity mice

"LOAEL – not established" is incorrect.

Response: As mentioned above, the Quast et al., 1990 (MRID 41651601) mouse oncogenicity study should be included in the evaluation of the potential carcinogenicity of nitrapyrin and the results from that study also should be reflected in this table. On the basis of both mouse carcinogenicity studies, **the LOAEL would be 75 mg/kg/day** and the NOAEL 25 mg/kg/day. No treatment-related increase in tumors was noted in any tissue at 75, 25 or 5 mg/kg/day.

Page 32, second line in table, 870.7600 Dermal penetration

"~26±6.4% recovered in the excreta in 24 hours. ~34±11% recovered after a total of 72 hours. Overall an estimate of dermal absorption in [sic] up to 46%."

Response: The study report (Domoradzki and Gibson, 1997; MRID 44282501) states that **24.58±6.43%** of the dose was absorbed at 24 hours following a single, dermal 24-hour exposure to Nitrapyrin. Thus, the value of "~26±6.4%" in this table is the wrong value as is the statement that this amount was "…recovered in the excreta..." Also, the overall estimate of 46% dermal absorption also is incorrect. The study report indicates that the 'overall' dermal absorption was **34.61±10.64%** at **72 hr** post-dosing.

9.2 Summary of Toxicological Dose and Endpoints for Nitrapyrin

Page 34, fourth line in table, Cancer (oral, dermal, inhalation)

The statement "Classified as "likely to be a carcinogen in humans" as per May 5, 2000 CARC report" **is believed to be incorrect**.

Response: As indicated above, the Scientific Advisory Group (Hardisty, 2004) concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

XII. OPP-2004-0283-0012. Reviews of a number of studies submitted in support of the reregistration of nitrapyrin. DP Barcode: D207458. May 25, 2004

At this time, Dow AgroSciences has no corrections or comments on this document.

XIII. OPP-2004-0283-0013. Nitrapyrin Chronic Dietary Exposure Assessment for the Reregistration Eligibility Decision. PC Code: 069203, DP Barcode: D299299. May 14, 2004

At this time, Dow AgroSciences has no corrections or comments on this document.

XIV. OPP-2004-0283-0014. Nitrapyrin – 1st Report for the Hazard Identification Assessment Review Committee. PC Code: 069203, TXR No. 0052387. March 1, 2004

2. Carcinogenicity Study in Mice

A. 1997 Study (From the Original DER)

Executive Summary

***Page 17, bolded text at end of first paragraph*:** The statements "LOAEL is 125 mg/kg/day, based on lesions in the liver (hepatocellular hypertrophy and single-cell necrosis) and digestive tract (hyperkeratosis and hyperplasia of the nonglandular stomach and epithelial cell vacuolation and hyperplasia/hypertrophy of the duodenum and jejunum in both sexes). The NOAEL was not determined." **represents only one study result and should not be regarded as correct without consideration of other relevant studies and information. The reviewers have not included all relevant studies and information in this assessment.**

Response: As mentioned elsewhere, the Quast et al., 1990 mouse oncogenicity study (MRID 41651601) should be included in the evaluation of the potential carcinogenicity of nitrapyrin and the results from that study also should be reflected in Table 4 of the HED chapter. **On the basis of both mouse carcinogenicity studies, the LOAEL would be 75 mg/kg/day and the NOAEL 25 mg/kg/day**. No treatment-related increase in tumors was noted in any tissue at 75, 25 or 5 mg/kg/day in the initial mouse oncogenicity study.

3. Classification of Carcinogenic Potential

Page 20, first paragraph: The statement "….nitrapyrin is classified as "likely to be a carcinogen in humans"….." **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the

HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by

Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

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The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003)

HAZARD CHARACTERIZATION

Page 20, seventh paragraph, Acute toxicity and sensitization: The statement " is not considered a dermal irritant (Toxicity Category III)……" should read … "(**Toxicity Category IV**)" as correctly listed in Table 3 of the HED Chapter.

Page 21, fourth paragraph, Carcinogenicity: The statement " Nitrapyrin is classified as "likely to be a human carcinogen….." **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not

include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related

hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003)

ACUTE TOXICITY

Page 24, last line in table: The statement "Classified as "likely to be a carcinogen in humans" **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD) has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic

response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report:

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003)

Page 21, footnotes in table: Footnote "a" states "Use 46% dermal adsorption factor for rout-to-route extrapolation." **This is incorrect**.

Response: As described in other sections, the incorrect value of "46%" for dermal absorption at "24 hours" is derived from series of misinterpretations, misreading and typographical errors. The study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 'overall' dermal absorption was **34.61±10.64%** at **72 hour** post-dosing. Furthermore, the study report states that **24.58±6.43%** of the dose was absorbed at **24 hours** following a single, dermal 24-hour exposure to Nitrapyrin.

XV. OPP-2004-0283-0015: Nitrapyrin: Team Review of Metabolism Information. PC Code: 069203, DP Barcode: 299923. February 23, 2004

It was confirmed through correspondence with Stephanie Plummer, EPA Chemical Review Manager, that **OPP-2004-0283-0015 is a duplicate document** to OPP-2004-0283-0005. Please refer to OPP-2004-0283-0005 for comments.

XVI. OPP-2004-0283-0016. Nitrapyrin RED – Reregistration Eligibility Decision: Product Chemistry Considerations. PC Code: 069203, DP Barcode: D295601. February 19, 2004

At this time, Dow AgroSciences has no corrections or comments on this document.

XVII. PP-2004-0283-0017: Memorandum; Nitrapyrin Use Closure Memo. June 27, 2004

At this time, Dow AgroSciences has no corrections or comments on this document.

XVIII. PP-2004-0283-0018. Nitrapyrin. Revised HED Chapter of the Registration Eligibility Decision Document (RED). PC Code: 069203, DP Barcode D298451. September 30, 2004

1.0 EXECUTIVE SUMMARY

Hazard Assessment

Page 5, fifth paragraph, lines 1 to 3: The statement "Dermal absorption value of 46% was bases on a rat dermal absorption study, to represent the residual chemical that could be absorbed." **is incorrect**.

Response: These values are not correct based on the study report (Domoradzki and Gibson, 1997; MRID 44282501) as well as Toxicology Chapter for the RED. The study report states that **24.58±6.43%** of the dose was absorbed at 24 hr following a single dermal **24 hr** exposure to Nitrapyrin (18% remained on the skin after washing at 24 hr and thus potentially was available for further absorption). At **72 hr** post-dosing, **34.61±10.64%** of the applied dose was absorbed (with 24.58% absorbed in the first 24 hr).

The HIARC report for Nitrapyrin (dated March 1, 2004) appears to be the source of the misleading dermal absorption value of 46%. The HIARC report (page 10) states that:

> *"…it was demonstrated nitrapyrin has a potential to remain on the skin following washing and this residual chemical can be absorbed to result in 34.6%±being absorbed over time. This high value of 46% represents the mean (~35%) plus the standard deviation (11)."*

There is no statistical or scientific basis for adding the standard deviation to the mean absorption value. The misleading value (of 46% dermal absorption) should be corrected in numerous text and footnote locations of the HED Chapter.

Examination of Table 7 of the dermal absorption study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 4 animals tested at 72 hr post-dosing had dermal absorption values of: 42.38, 19.30, 35.48, and 41.27% resulting in a mean value of 34.61% and a standard deviation of 10.64%. Obviously, the relatively large standard deviation primarily is due to the low value of 19.30% for one animal and reflects significantly lower absorption than the other animals. Thus, in contrast to the HIARC process of adding the standard deviation to the mean value to derive a dermal absorption value of ~46%, a more reasonable process would be to subtract the standard deviation from the mean value. However, the important point is that **the HED Chapter should reflect the actual dermal absorption study results** of **34.61±10.64%** at **72 hr** post-dosing.

Page 6, fifth paragraph, line 1: The statement "Nitrapyrin is classified as "likely to be a human carcinogen…." **is believed to be incorrect**.

Response: As indicated above, the Scientific Advisory Group (Hardisty, 2004) concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in

individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Page 14, second paragraph, Dermal Absorption: The statement "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." **is incorrect**.

Response: These values are not correct based on the study report (Domoradzki and Gibson, 1997; MRID 44282501) as well as Toxicology Chapter for the RED. The study report states that **24.58±6.43%** of the dose was absorbed at 24 hr following a single dermal **24 hr** exposure to Nitrapyrin (18% remained on the skin after washing at 24 hr and thus potentially was available for further absorption). At **72 hr** post-dosing, **34.61±10.64%** of the applied dose was absorbed (with 24.58% absorbed in the first 24 hr).

The HIARC report for Nitrapyrin (dated March 1, 2004) appears to be the source of the misleading dermal absorption value of 46%. The HIARC report (page 10) states that:

> *"…it was demonstrated nitrapyrin has a potential to remain on the skin following washing and this residual chemical can be absorbed to result in 34.6%±being absorbed over time. This high value of 46% represents the mean (~35%) plus the standard deviation (11)."*

There is no statistical or scientific basis for adding the standard deviation to the mean absorption value. The misleading value (of 46% dermal absorption) should be corrected in numerous text and footnote locations of the HED Chapter.

Examination of Table 7 of the dermal absorption study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 4 animals tested at 72 hr post-dosing had dermal absorption values of: 42.38, 19.30, 35.48, and 41.27% resulting in a mean value of 34.61% and a standard deviation of 10.64%. Obviously, the relatively large standard deviation primarily is due to the low value of 19.30% for one animal and reflects significantly lower absorption than the other animals. Thus, in contrast to the HIARC process of adding the standard deviation to the mean value to derive a dermal absorption value of ~46%, a more reasonable process would be to subtract the standard deviation from the mean value. However, the important point is that **the HED Chapter should reflect the actual dermal absorption study results** of **34.61±10.64%** at **72 hr** post-dosing.

Page 14, third paragraph, Carcinogenicity: The statement "….A classification of "likely to be carcinogenic to humans" was assigned by the Cancer Assessment Review Committee (CARC) dated May 5, 2000, using the criteria in the Draft Guidelines for Carcinogen Risk Assessment (July, 1999)."……. "Subchronic, chronic and other types of toxicity studies are summarized in Table 4."….. **is believed to be incorrect based on incomplete information**.

Response: The reviewers have not included all relevant studies and information in the cancer assessment review and, on that basis, the Agency should reconsider the proposed cancer classification of nitrapyrin. Specifically, the CARC report (May 5, 2000) does not include the results of the Quast et al., 1990 (MRID 41651601) mouse carcinogenicity study. This valid study demonstrates an absence of treatment-related tumors at reasonable dose levels and thus provides key information for the evaluation of tumor mechanism and tumor dose response. The changing scientific and regulatory position on dose level selection for carcinogenicity studies (i.e., maximum tolerated dose; MTD)

has been an issue for Nitrapyrin and the exclusion of the earlier mouse carcinogenicity by the Agency obscures the resolution of this issue. To this point, the May, 2000 CARC report preceded the promulgation of the HED Interim Guidance Document (# G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003. Also, the CARC report indicates "…the available mutagenicity data are supportive of a mutagenic mode of action…" based on chemical structure and a non-guideline, non-GLP mutagenicity study while also dismissing the negative results of all guideline, GLP studies submitted to the Agency by the Registrant. The CARC opinion contrasts with the HED chapter statement (page 13) that "There is no mutagenicity concern with nitrapyrin."

The mouse carcinogenicity study by Quast et al., 1990 (MRID 41651601) provides information that is critical in the evaluation of the dose response as well as possible tumor mechanisms at higher dose levels. This study with B6C3F1 mice provided dietary administration at reasonable dose levels of 0, 5, 25 or 75 mg nitrapyrin/kg body weight/day for two years. These lower dose levels did not result in an oncogenic response in any organ or tissue. In addition, these dose levels did not cause hepatocellular necrosis or hyperplasia of the nonglandular mucosa of the stomach.

In contrast to the earlier mouse carcinogenicity study (Quast et al., 1990; MRID 41651601), the hepatocellular necrosis and hyperplasia of the nonglandular mucosa of the stomach observed in the mice treated with 125 or 250 mg Nitrapyrin/kg/day in the subsequent mouse carcinogenicity study (Stebbins and Cosse, 1997; MRID 44231803) predisposed the liver and stomach to tumorigenesis. Chronic dietary administration of Nitrapyrin to mice at these dose levels exceeded the MTD based on treatment-related hepatocellular necrosis and the associated compensatory hepatocellular proliferation. In addition, body weight gains were decreased 26-33% relative to controls over much of the dosing period. This study was required by the Agency based on an early 1990s' MTD policy and thus, the predictable tumor results of the study should be interpreted in light of current scientific understanding as described in the HED Interim Guidance Document (#

G2003.02) "Rodent Carcinogenicity Studies; Dose Selection and Evaluation," dated July 1, 2003.

A scientific review of the 2-year, mouse carcinogenicity study with Nitrapyrin (Stebbins and Cosse, 1997; MRID 44231803) as well as other relevant studies recently has been conducted by independent expert pathologists (a Scientific Advisory Group) and submitted to the Agency during the 60-day public comment period (as requested by Stephanie Plummer, EPA Chemical Review Manager) for the reregistration process for nitrapyrin in the following report::

> Hardisty, J.F. "A Histopathology Peer Review and Scientific Advisory Group (SAG) Review of Potential Target Organs (Liver, Forestomach, Harderian Gland and Epididymis) and Mode of Carcinogenic Action," Experimental Pathology Laboratories, Inc., November 22, 2004.

The Scientific Advisory Group concluded that nitrapyrin-induced tumor formation in mice was likely via a nongenotoxic, cytotoxic mode of action at dose levels that exceeded the Maximum Tolerated Dose. Thus, exposure conditions that do not produce target organ toxicity in individuals would not be expected to increase the risk of cancer in humans. This assessment along with the lack of relevant treatment-related tumors in the two-year rat bioassay and the lack of concern for mutagenicity or genetic toxicity indicates that Nitrapyrin should be classified as "Not Likely to Be Carcinogenic to Humans" according the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001A, February, 2003).

Page 16, fourth line of Table 4, 870.4200 Carcinogenicity mice:

The statements "NOAEL < 125 mg/kg/day…." and "LOAEL – not established." **are incorrect**. **The reviewers have not included all relevant studies and information in this assessment.**

Response: As mentioned above, the Quast et al., 1990 mouse oncogenicity study (MRID 41651601) should be included in the evaluation of the potential carcinogenicity of nitrapyrin and the results from that study also should be reflected in Table 4 of the HED chapter. **On the basis of both mouse carcinogenicity studies, the LOAEL would be 75 mg/kg/day and the NOAEL 25 mg/kg/day**. No treatment-related increase in tumors was noted in any tissue at 75, 25 or 5 mg/kg/day in the initial mouse oncogenicity study.

Page 18, first line of Table 4, 870.7600 Dermal penetration: The statements "~26±6.4% recovered in the excreta in 24 hours. ~34±11% recovered after a total of 72 hours. Overall an estimate of dermal absorption in [sic] up to 46%." **are incorrect.**

Response: As mentioned above, the study report (Domoradzki and Gibson, 1997; MRID 44282501) states that **24.58±6.43%** of the dose was absorbed at 24 hours following a single, dermal 24-hour exposure to Nitrapyrin. Thus, the value of "~26±6.4%" in Table 4 is the wrong value as is the statement that this amount was "…recovered in the excreta..."

Also as described above, **the overall estimate of 46% dermal absorption also is incorrect**. The study report indicates that the 'overall' dermal absorption was **34.61±10.64%** at **72 hr** post-dosing.

3.3 Dose Response Assessment

Page 18, Dermal Absorption Factor (first part of paragraph): The statements "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 exposure. 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." **are incorrect.**

Response: The results of the Nitrapyrin 21-day repeated dose dermal toxicity study in rabbits (Cosse et al., 1992: MRID 42239301) **demonstrate target organ effects in the liver that are consistent with the findings following oral exposures in mice, rats, rabbits and dogs.** The study results indicate statistically significant increases in absolute and relative liver weights in rabbits following 21 days of dermal treatment with 1000 mg Nitrapyrin/kg/day. **Thus, the increased liver weights following dermal exposure to rabbits contradict a conclusion that "…the rabbit is a poor model for assessing dermal toxicity**."

Pages 18 and 19, Dermal Absorption Factor (last part of paragraph): The statement "…whereas a dermal absorption study in rats indicate 46% dermal absorption at 24 hours…. 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." **is incorrect**.

Response: As described above, the incorrect value of "46%" for dermal absorption at "24 hours" is derived from series of misinterpretations and typographical errors. The study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 'overall' dermal absorption was **34.61±10.64%** at **72 hour** post-dosing. Furthermore, the study report states that **24.58±6.43%** of the dose was absorbed at **24 hours** following a single, dermal 24-hour exposure to Nitrapyrin.

Page 20, Table 5, footnote 'a': The statement "a = low absorption via the dermal route, which was not demonstrated in the dermal rabbit study, would indicate the rabbit is a poor model for assessing dermal toxicity…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" **is incorrect.**

Response: The same rationale presented in comments for 'Page 18, Dermal Absorption Factor (first part of paragraph)' and 'Pages 18 and 19, Dermal Absorption Factor (last part of paragraph)' applies here:

The results of the Nitrapyrin 21-day repeated dose dermal toxicity study in rabbits (Cosse et al., 1992: MRID 42239301) **demonstrate target organ effects in the liver that are consistent with the findings following oral exposures in mice, rats, rabbits and dogs.** The study results indicate statistically significant increases in absolute and relative liver weights in rabbits following 21 days of dermal treatment with 1000 mg Nitrapyrin/kg/day. **The increased liver weights following dermal exposure to rabbits contradict a conclusion that "…the rabbit is a poor model for assessing dermal toxicity**."

As described above, the incorrect value of "46%" for dermal absorption at "24 hours" is derived from series of misinterpretations and typographical errors. The study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 'overall' dermal absorption was **34.61±10.64%** at **72 hour** post-dosing. Furthermore, the study report states that **24.58±6.43%** of the dose was absorbed at **24 hours** following a single, dermal 24-hour exposure to Nitrapyrin.

7.0 Occupational Exposure

7.3 Cancer Handler Exposure/Risks

Page 33, bullet point 4: The statement "Dermal absorption is assumed to be **46%**..." **is incorrect.**

Response: The same rationale presented in comments for 'Page 18, Dermal Absorption Factor (first part of paragraph)' and 'Pages 18 and 19, Dermal Absorption Factor (last part of paragraph)' applies here:

The results of the Nitrapyrin 21-day repeated dose dermal toxicity study in rabbits (Cosse et al., 1992: MRID 42239301) **demonstrate target organ effects in the liver that are consistent with the findings following oral exposures in mice, rats, rabbits and dogs.** The study results indicate statistically significant increases in absolute and relative liver weights in rabbits following 21 days of dermal treatment with 1000 mg Nitrapyrin/kg/day. **The increased liver weights following dermal exposure to rabbits contradict a conclusion that "…the rabbit is a poor model for assessing dermal toxicity**."

Response: As described above, the incorrect value of "46%" for dermal absorption at "24 hours" is derived from series of misinterpretations, misreading and typographical errors. The study report (Domoradzki and Gibson, 1997; MRID 44282501) indicates that the 'overall' dermal absorption was **34.61±10.64%** at **72 hour** post-dosing. Furthermore, the study report states that **24.58±6.43%** of the dose was absorbed at **24 hours** following a single, dermal 24-hour exposure to Nitrapyrin.