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April _____, 2004

Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program
Response to Comments
AR-201-14391
Mononitroanilines Category
o-nitroaniline, CAS No. 88-78-4
p-nitroaniline, CAS No. 100-01-6

We are pleased to provide the Agency our responses to comments received from EPA and other stakeholders on our referenced HPV Chemical Challenge submission for the Mononitroanilines Category, which you will find attached. We are forwarding responses to the specific comments, along with a revised Test Plan and Robust Summary package.

Thank you for your consideration. Please contact me directly should there be any question related to this submission.

Sincerely,

Regards,

Donald A. Lederer, CHMM
Product Stewardship Manager

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Response to Comments on HPV Challenge Submission

Mononitroanilines Category

CAS Number 88-74-4; 2-nitroaniline

CAS Number 100-01-6; 4-nitroaniline

EPA Comments

Specific Comments on the Test Plan

COMMENT 1: *Vapor pressure.* With regard to PNA, the Dixon and Rissman (1985) citation does not include the primary source for the cited values; therefore, they cannot be identified as either measured or calculated. Furthermore, the value provided by the submitter does not agree with a measured value for ONA found by EPA, 0.0000032 mm Hg (Ferro, D. and Piacente, V. Heat of vaporization of o-, m-, and p-nitroaniline. *Thermochim Acta* 90: 387-9 (1985)). The submitter needs to verify this value.

RESPONSE: The secondary literature for the vp of the nitroanilines appears to be confused as no measurements of vapor pressure were taken by Ferro and Piacente at ambient temperatures. The original Ferro and Piacente paper was obtained and robust summaries were prepared for both compounds after extrapolation of the measured data (taken at higher temperatures) to 25°C. The robust summaries contain the equation relating vapor pressure and the calculations used to extrapolate the vapor pressure to 25°C

The extrapolated values using data from the original source are in the table below:

Chemical	Vapor Pressure @ 25° C.	
	(hPa)	(mm Hg)
ONA (solid)	0.00115	0.0086 mm
PNA (solid)	0.0000042	0.0000032

COMMENT 2: *Biodegradation.* Although ready biodegradability tests are not available, in this case the data presented by the submitter are adequate for the purposes of the HPV Challenge Program. While the PNA SCAS test data suggest some biodegradability, the nature of the test, the results obtained, and certain observations in the course of the study suggest that PNA, like ONA, will resist biodegradation (the robust summary indicates

that PNA appeared to be moderately degradable; that the data obtained were somewhat erratic; that during the last two months of testing, far lower rates were observed: and that substantial inhibition of the normal sludge growth rate occurred). EPA located data confirming that PNA is not significantly biodegradable: (1) 0% ThBOD in 14 days (OECD 302C; Ref. 1); (2) degradation in > 64 days (screening study with soil inoculum, aerobic; Ref.2).

The submitter incorrectly states that PNA is "readily biodegradable". Ready biodegradability cannot be inferred from positive results in an inherent biodegradability test. The submitter needs to correct its conclusion.

RESPONSE:

We agree that information sufficient for the needs of the HPV program concerning biodegradation of these two materials is available. In the case of ONA, both our SCAS data and several literature citations support resistance to biodegradation.

In the case of PNA, however, there are conflicting reports concerning biodegradation potential. Both our SCAS test and two other literature reports support biodegradation of PNA at low concentration levels. These have been incorporated into the test plan with full discussion concerning possible mechanisms. Although it cannot be inferred that PNA would be classified as "readily biodegradable", it appears likely that biodegradation can be fairly rapid under the correct set of conditions.

A complete discussion of this and the older literature has been added to the Test Plan. The robust summaries were revised to reflect reinterpretation of the PNA data.

Additional references were added to the ONA robust summary supporting the study, the range of 24-hour biodegradation was corrected and the conclusion was changed from "no" to "little evidence of biodegradation"

FUGACITY: The revisions to the vapor pressure and the biodegradation sections invalidated the fugacity determinations. Fugacity was recalculated using the revised values and assuming that all material would be released to water because this is considered to be the most likely industrial environmental release. The revised calculations indicate that the mononitroanilines will remain almost exclusively in water with a small quantity (less than 1%) distributing to sediment.

COMMENT 3: *Repeated-dose toxicity.* The test plan misstated the results for systemic toxicity of ONA (text section 2.0, third paragraph, line 11-12). Hematological changes were significant in both sexes, as correctly noted in lines 14-16 in the same paragraph.

RESPONSE:

The "misstatement" referred to could not be located. The sentence that appears to be in question is a statement about the reliability of the results and not a statement of the results.

No changes were made.

COMMENT 4: *Reproductive toxicity.* No data were submitted for ONA. The adequacy of a two-generation study on PNA cannot be determined because of the lack of an effective dose. The highest dose tested, 9 mg/kg/day, was the NOAEL. The submitter can nonetheless satisfy the reproductive toxicity endpoint by describing in robust summary format the reproductive histopathology from the PNA 90-day repeated-dose assay results. The submitter's plan to use a read-across approach for this endpoint is justified on the basis of generally similar toxic effects of ONA compared to PNA.

RESPONSE:

Results of the microscopic examination of reproductive organs from the 90-day study were unremarkable and have been added as a separate robust summary in the reproductive toxicity section. It was concluded that the NOAEL for reproductive organs was 30 mg/kg-day while the 3 mg/kg-day dose was a systemic LOAEL with blood and spleen affected. This 90-day reproductive-organ information combined with the adequate developmental toxicity study and the 2-generation study (which has been slightly reinterpreted as indicated below) is considered to adequately fill the reproductive toxicity endpoint for the HPV program.

In addition, the individual pathology data from the 2-Generation study was examined in detail for signs of adverse effects on the spleens of F1 animals at sacrifice (when their pups were weaned). Minimal amounts of "brown pigment" were reported in 1/10 males and moderate amounts of brown pigment were reported in 3/10 females. Although the original study authors did not flag this effect as being compound related, it appears that 9 mg/kg-day can be considered a LOAEL for systemic toxicity for the females with the effect being marginal in the males. In light of the 90-day gavage findings, the effects on the spleens of treated rats take on higher significance and can be used to establish the mid-dose of 1.5 mg/kg-day as the NAOEL (adult) in this 2-generation study.

The reproductive endpoint for ONA is filled by the read-across approach based on the similar toxicity of these two materials.

COMMENT 5: *Developmental toxicity.* The submitter needs to provide more information on maternal toxicity in the ONA study so that the discrepancy in the NOAELs among the test plan (Table 9), robust summary, and repeated-dose assays can be addressed.

RESPONSE:

The robust summary misstated information relative to determination of the maternal ONA NOAEL. The correct information was obtained from the laboratory report and has replaced the misstated information in the updated robust summary. Please see the response to the comments on the individual robust summaries below (Comment 9) for a full explanation.

COMMENT 6: *Algae.* EPA disagrees with the submitter that the algal tests were conducted according to OECD, EPA, or ASTM test guidelines for this endpoint, and considers the two submitted algal studies inadequate and of limited value. A 72- or 96-hour test duration for algae is required before a determination of data adequacy can be rendered.

RESPONSE:

The duration of the algae inhibition test was less than guideline specifications; however, it is considered an adequate demonstration of low algal hazard. In deference to the Agency and with realization of the short duration of the studies presented in the Test Plan and Robust Summaries, the literature was searched for studies of guideline duration. A 96-hour study of algal growth inhibition was found for PNA and has been included in the Robust Summaries as the “critical” study. The previous two studies remain in the document as supporting data for the reported inhibition value and to support the validity of assessing algal growth inhibition of ONA using the “read across” approach.

The test plan has also been revised to show this new value and specify that ONA algal growth inhibition is assessed using a “read-across” approach in combination with 48-hour data supporting the “read across”

The guideline compliance has been modified to be more appropriate.

Specific Comments on the Robust Summaries

COMMENT 7: Of twelve of health effects robust summaries, none gave the full chemical name of the test material.

RESPONSE:

Robust summaries have been modified to identify the test substance either by the full chemical name and CAS Number, or by the generally accepted acronym, PNA for p-nitroaniline and ONA for o-nitroaniline.

COMMENT 8: *Reproductive toxicity.* A robust summary for a two-generation gavage assay in rats for PNA provided sufficient information to evaluate the study methods, but was missing details about the results that would be needed to verify the study NOAEL and the overall study adequacy (which depends upon the administration of an effective dose).

RESPONSE:

The individual pathology data from the study was examined in detail for signs of adverse effects on the spleens of F1 animals at sacrifice (when their pups were weaned). Minimal amounts of “brown pigment” were reported in 1/10 males and moderate amounts of brown pigment were reported in 3/10 females. Although the original study authors did not flag this effect as being compound related, it appears that 9 mg/kg-day can be considered a LOAEL for systemic toxicity for the females with the effect being marginal in the males. In light of the 90-day gavage findings, the effects on the spleens of treated rats take on higher significance and can be used to establish the mid-dose of 1.5 mg/kg-day as the NAOEL (adult) in this 2-generation study.

A separate paragraph giving this result has been added to the robust summary and the NOAEL (parental) has been lowered from 9 mg/kg to 1.5 mg/kg in response to this reinterpretation.

The information in the appropriate Test-Plan Table was also changed to reflect this new interpretation.

COMMENT 9: *Developmental toxicity.* The summary for the study on ONA provided sufficient information to verify the validity of study methods, but did not provide sufficient information on maternal toxicity (especially clinical signs) to verify the assignment of the NOAEL; the summary assigned a higher NOAEL than Table 9 of the test plan, but it is possible that both are incorrect, and that the lowest dose was the NOAEL. Providing data from a pilot range-finding study could help support this study.

RESPONSE:

The robust summary misstated information relative to determination of the maternal ONA NOAEL. The correct information was obtained from the laboratory report and has replaced the misstated information. The maternal NOAEL is considered to be 100 mg/kg based on body-weight gains and clinical signs. Food consumption data were less informative. Although data from the pilot study are available the dose levels were different and it is difficult to compare. In addition, since it is more appropriate to use concurrent maternal data, data from the pilot study have not been added. The data in the Test-Plan Table has been updated to reflect the robust summary information. Although there were some slight fetal effects at 300 mg/kg, they were not statistically or biologically significant. The criteria used for determination of maternal and fetal toxicity are now congruent and the results clearly support a lack of developmental toxicity for ONA.

COMMENT 10: *Algae.* Water hardness is the only missing data element for ONA, and needs to be submitted if available.

RESPONSE:

Water hardness was not provided as such. The formula for the algal growth media is supplies in the published reference.

Environmental Defense Comments

COMMENT 11: The sponsor claims that ONA and PNA have been shown to act through a common mode of action. While we agree that the category is justified, existing data only demonstrate a common pattern of toxic effects. No data were presented on the biological processes which cause those effects. For example, no metabolism or gene expression data were presented in the test plan or robust summary. Although this category appears well-behaved, both metabolism and gene expression data could significantly increase confidence in the validity of this proposed category, and more generally.

RESPONSE:

Although we agree that metabolism and gene-expression data would be a useful addition to the document, little definitive information of this type is available. In addition, it is beyond the scope of the HPV program requirements to extensively discuss metabolism for compounds where the toxic end-points are already clearly delineated and where the categorical structural relationships are clear.

Animal Protection Organizations Comments

No responses necessary