To: Adam Jonas, Ph.D.
Lucebni zavody Draslovka a.s. Kolin
Kavlickova 606, 280 02 Kolon IV
Czech Republic

Re: Ethanedinitrile (cyanogen; CAS 460-19-5)

The purpose of this document is to briefly summarize the methodology used by the United States Environmental Protection Agency (US EPA) in its Human Health Risk Assessment for cyanide (2006). This risk assessment was done for purposes of issuing a Tolerance Reassessment Eligibility Decision (TRED) Document for use of this active ingredient on citrus as a post-harvest fumigant. This assessment, and the methodology used, are relevant to Ethanedinitrile since the toxicity of this molecule is predominantly due to cyanide ions which readily dissociate from the parent material.

This comprehensive Human Health Risk assessment was conducted by the Health Effects Division (HED), which resides in US EPA's Office of Pesticide Programs (OPP). OPP/HED's scientists are responsible for evaluating all conventional chemical pesticide products, and they can also provide support for the evaluation of other agricultural products such as biopesticides. It should be noted OPP/HED has significantly greater resources and overall expertise than the IRIS program.

In the US EPA human health risk assessment, toxicology data on all forms of cyanide were used; this included toxicology data from some cyanogenic molecules such as cassava, acetone cyanohydrin, and Ethanedinitrile.

The US EPA specifically used the Lewis *et. al*. (1984) study which they Classified as an "Acceptable/Non-guideline" study, indicating that the Agency did not have significant concerns with the quality of the study. [Note: this is the same Classification that US EPA gave to some acetone cyanohydrin studies done by the Monsanto Company's Toxicology Laboratory where I was employed in the Inhalation Toxicology Group during the timeframe when those studies were conducted.] The Agency concluded that the results at 25 ppm cyanogen suggest that the subchronic exposures were only marginally toxic, and that the 11 ppm cyanogen exposure was considered to be a no adverse-effect level (NOAEL).

In the US EPA Human Health Risk Assessment, the Agency develops a variety of Hazard Identification and Toxicity Endpoint Selection assessments. For purposes of

this document, only those considering Inhalation Exposure are considered here since that is the way by which humans are potentially exposed to Ethanedinitrile.

For their "Inhalation Exposure (All Durations)" assessment, the US EPA's endpoint was selected based on a subchronic inhalation toxicity study in rats. In this study, Sprague-Dawley rats (15/sex/dose) were exposed to acetone cyanohydrin (ACH) [which is rapidly hydrolyzed to to hydrogen cyanide at physiological pH] at concentrations of 0, 36, 101, or 204 mg ACH/m^3 for 6 hours/day, 5 days/week for 14 weeks. The exposures were equivalent to 0, 11, 32, and 65 mg HCN/m^3.

Dose/Endpoint for Risk Assessment: The US EPA determined that the NOAEL in that study was 65 mg HCN/m^3. For occupational exposure, the inhalation study NOAEL of 65 mg HCN/m3 (60 ppm) would be converted to a human equivalent dose of 50 mg HCN/m3 (65 mg HCN/m3 x (6h/8h) assuming similar Regional Gas Distribution Ratio (RGDR) between animals and humans.

Comments about Study/Endpoint: The NOAEL/LOEL for the inhalation endpoint was based on the effect of mortality for hydrogen cyanide. The Margin of Exposure (MOE) was based on the uncertainty factor of 30X (3X interspecies factor and 10X intraspecies factor). The traditional interspecies factor of 10X was reduced to 3X since the doses are expressed as air concentrations and the pharmacokinetics was assumed to be similar between animals and humans. The interspecies factor of 3X was considered sufficient to account for only pharmacokinetic differences between animals and humans. An additional 10X for steepness of dose response/severity of effect was considered unnecessary due to the conservative nature of the selected endpoint, i.e., a subchronic exposure is use endpoint was used to assess intermittent short-term exposure.

Hypothetical US EPA Risk Assessment for EDN:

If the US EPA conducted a risk assessment for ethanedinitrile using:

(a) the study/point-of departure identified by the NZ EPA (Lewis *et. al*., 1984),
(b) an 11 ppm NOAEL from that study,
(c) EPA's calculation of human equivalent dose,
(d) and an overall 30X uncertainty factor (as was done for cyanide),

then the the resulting acceptable exposure level would be 0.275 ppm (11 ppm x 6/8 / 30).

If US EPA would decide that an additional uncertainty factor needs to be included for lack of a robust dataset, a factor of '2' or '3' is typically utilized, and the resulting acceptable exposure levels would be 0.137 ppm or 0.0917, respectively.

Conclusion:

An occupational risk assessment for ethanedinitrile based on results from the Lewis *et. al*. (1984) study and the methodology employed in the US EPA's cyanide risk assessment would result in acceptable exposure levels in the range of approximately 0.1 ppm to 0.27 ppm ethanedinitrile.

William F. Heydens, Ph.D.
IGET Advisor, LLC
Toxicology & Human Health Risk Assessment Advisor

REFERENCE:

Sodium Cyanide Revised HED Risk Assessment for Tolerance Reassessment Eligibility Decision (TRED) Document PC Code No. 074002; DP Barcode No. 318015. July 10, 2006. Becky Daiss through Susan V. Hummel to Wilhelmena Livingston. United States Environmental Protection Agency, Washington, D.C. 20460.