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Derivation of a Tolerable Exposure Level (TEL) for Chronic Exposure to Ethanedinitrile the Active in EDN (APP202804)

Issue

The EPA has proposed a tolerable exposure level (TEL) for the chronic exposure to ethanedinitrile at a level of 0.036 ppm (EDN Science Memo, APP202804). Whereas, the Applicant has proposed a value of 0.56 ppm (Draslovka 2018). Both the EPA and the Applicant based their values using the results of the study by Lewis,1984. The difference in values is a result of the EPA using an uncertainty factor of 100 while the Applicant used a value of 6 in calculating their TEL value.

Background

The tolerable exposure level (TEL) is an environmental concentration of a chemical which is deemed as being a “safe level” for the general public to be exposed to on a continuous (24 hr) basis every day over a lifetime without significant risk for harm. The TEL is calculated by dividing the no-observed-adverse-effect-level (NOAEL) dose from the most pertinent toxicology study for the chemical of concern by various assessment or uncertainty factors (UF) to account for various scientific uncertainties and variabilities in order to establish an exposure that ensures protection of the most sensitive individuals in the target population.

For ethanedinitrile, the most pertinent toxicity study chosen by both the EPA and the applicant was a study by Lewis, 1984. In that study rodents and primates were exposed to ethanedinitrile gas for six months at levels of 11 and 25 ppm. The most sensitive species in that study appeared to be the rat based on a significant decrease in final body weight at study termination at the higher exposure level (NOAEL 11 ppm). The atmospheric NOAEL in rats was subsequently converted to a mg/kg bw/day dose based on their daily intake of the gas using default respiratory physiological parameters. This conversion allows for the normalisation of the exposure concentration to compensate for differences between rodents and humans relative to their daily air intake (m^3)/kg bw. After calculating an estimated safe mg/kg bw/day allowable daily intake (ADI; NOAEL/UF), the reverse calculation was completed to convert the “safe” mg/kg bw/day dose back into the atmospheric ppm level that would deliver that mg/kg dose to a human using default human respiratory air intake parameters. For this study, the EPA calculated a NOAEL dose of 2.05 mg/kg bw/day in rodents based on the 11.2 ppm exposure. Based on this NOAEL and standard risk assessment methodologies to develop UF, the EPA then divided this dose by a 100 fold UF and back converted it into an atmospheric concentration to derive a TEL of 0.036 ppm ethanedinitrile gas. The Applicant also conducted a TEL calculation using the same NOAEL

but derived a TEL of 0.56 ppm (Draslovka). The difference being they used an UF denominator of 6.

Uncertainty factors are used in toxicology risk assessments to account for numerous concerns associated with extrapolating hazards identified in laboratory animal data to risks for humans. The difference between the TEL value derived by the EPA and the Applicant are a result of the dissimilarities in the total number of UF utilised and the magnitude of the UF utilised. Typically UF vary from 1 -10 for different endpoints of concern (discussed more below). Specifically in this scenario, the EPA adjusted the NOAEL by 100 through the use of five different UFs and the Applicant utilised two different UFs that totalled 6. In the setting of the TEL, the EPA also took into account the chronic exposure values already established by numerous other regulatory agencies or authoritative bodies which have set such levels for cyanide as the toxicity of ethanedinitrile is believed to be mediated through its conversion in animals to cyanide.

Historically, the UF of 100 was introduced in 1954 in the US in response to legislative guideline needs for establishing a safe dose of food additives (Lehman and Fitzhaugh, 1954). This approach proposed that a safe level of food additives or contaminants could be derived by dividing the NOAEL from chronically exposed animals by a factor of 100. Overtime, it has been determined that this conventionally used default factor of 100, which basically consisted of a 10-fold factor to account for uncertainties associated with extrapolating data from animals to humans (intraspecies) and a 10-fold factor to account for interspecies variation or sensitivities amongst humans, could be refined based on more knowledge associated with the chemical of concern. In addition to the intraspecies uncertainties and interspecies variabilities, other UFs needed to be added to account for study and data base issues such as:

1. Uncertainties associated with extrapolating oral exposure data to inhalation risks, or vice-versa (i.e., different route-to-route exposure uncertainty extrapolations)
2. Extrapolating data where a NOAEL is not established, i.e., needing to go from a lowest-observed-adverse-effect-level (LOAEL) to a NOAEL
3. Extrapolating data from shorter-term exposure studies to assess risks for chronic exposures.
4. Uncertainties to account for deficiencies in the total database and an inability to account for all potential hazards, i.e., data gaps
   and
5. Robustness or deficiencies in the key study used to establish the NOAEL, often called a modifying factor rather than an uncertainty factor.

The original 10X UF for making extrapolations between the test system (laboratory animals) and the target population (humans)(i.e., interspecies) and for accounting for variations in different sensitivities in the human population (i.e., intraspecies) have been further refined through the use of knowledge on species differences in absorption, distribution, metabolism and excretion (i.e., toxicokinetic adjustments; TK), and on known differences between species or individuals in their reactions to the toxic material(i.e., toxicodynamic adjustments; TD). Such refinements are especially pertinent for intraspecies difference between humans to account for extra sensitivities associated with fetuses, neonates, children, elderly and genetically sensitive subgroups which may be particularly vulnerable and may be present in the targeted general population.

The EPA, as well as many other global regulatory agencies have derived uncertainty assessment factors of various magnitudes to compensate for these aforementioned data gaps and variabilities (Table 1). According to the defined methodology formerly set out in NZ legislation the product of the UF must not be less than 1 and not more than 10,000. [Note: This legislation has sense been revoked and does not have statutory significance anymore and is only noted as a historical methodological reference.] Similarly, the USA EPA stipulates an UF product range that may vary from 1 to 3000 depending on data robustness.

Derivation of the TEL and Assignment of Uncertainty Factors by the EPA and the Applicant (Table 1)

1.) **Interspecies (laboratory animal to human) uncertainties**

EPA: 4

Applicant: 2

Although the default UF is 10 (unless TK and TD factors are considered) the EPA utilized a factor of 4. A factor of 4 is the default value used in the REACH technical guidance document and by ECETOC and WHO/IPCS to account for TK and metabolic differences between species. The quantitative TK of ethanedinitrile (i.e., its uptake and lung absorption, and its metabolism and excretion) in both laboratory animals and humans are unknown so there is no way to directly compare plasma concentration and effects between species. Although it is highly believed that the acute lethality of ethanedinitrile is mediated through its breakdown to cyanide, the absence of specific knowledge in regard to the TK of ethanedinitrile gas from inhalation exposures decreases the confidence and ability to directly correlate its potential sequelae from chronic exposures between species. In general, the main TD concern of chronic cyanide exposure in humans is

disruption of thyroid metabolism from its detoxification to thiocyanate. Importantly, this effect appears to not have been manifested in the Lewis study. However, the EPA is concerned with the fact that different forms of cyanides (organic and inorganic) also appear to be capable of inducing different types of toxicities (e.g., kidney and CNS effects) with less known modes of action; and that there are different NOAELs in studies of similar duration from different cyanide forms. Thus different types of cyanides seem to manifest in different types of toxicity when exposed chronically. It is also unknown as to what the etiological basis was for the significant weight loss effect observed in the Lewis study rats and what it may correlate to in humans.

The Applicant utilised an interspecies uncertainty factor of 2 based on the NRC 2001 reference that established acute exposure guidelines (AEGL) for hydrogen cyanide to the general public for different exposure durations (10 min. to 8 hrs) and toxicity scenarios (AEGL-1 minimal effects, AEGL -2 acutely incapacitating, and AEGL-3 lethality). This is made evident by the toxicity studies used for each endpoint. Such that an UF of 1 was used for the AEGL-1 based on subjective symptoms in humans (i.e., no animal to human extrapolation was needed). The AEGL-2 used a toxicity endpoint based on slight nervous system depression in monkeys following a 30 minute high level exposure and had an interspecies factor of 2 because both primates and humans are relatively similar in their responses to this effect. The AEGL-3 interspecies UF was 2 because the LC_{50} values among different animal species differed by less than a factor of 2. The EPA is of the position that because the interspecies UF utilised by the Applicant was developed for the establishment of safe acute exposure situations it is not applicable to the uncertainties and concerns associated with establishing safe chronic exposure levels.

2.) Intraspecies variation (differences and sensitivities within the human population)
EPA: 5
Applicant: 3

Although the default UF is 10 (unless TK and TD factors are considered) the EPA utilized a factor of 5 as defined by ECETOC as insufficient information is available to quantitatively estimate the variability in human susceptibility to chronic ethanedinitrile exposure and the TK and TD of ethanedinitrile in humans is also unknown.

The Applicant utilised an intraspecies uncertainty factor of 3 (NRC 2001, see AEGL discussion in category 1 above). Again, the EPA is of the position that the basis for their UF is not relevant as it related only to the protection of lethality from acute exposure

situations and does not necessarily apply to the uncertainties and concerns associated with establishing safe chronic exposure levels. The UF of 3 is used to account for human variability in rhodanase detoxification enzyme levels (NRC 2001). This is important to protect against acute lethality should its capacity get overwhelmed. The importance of the variability in rhodanase levels for protecting against chronic toxicity endpoints is much less pertinent as there is a negligible chance of it being saturated from low-level exposures. The toxicity and mode of action manifested from chronic cyanide exposure is different than that from an acute exposure and thus the basis for and magnitude of the UF needs to be different. The primary concern of chronic cyanide toxicity is associated with the cyanide detoxification metabolite thiocyanate. The effect of the thiocyanate metabolite on human thyroid function triggers a wide range of concerns in fetuses, children, and adults with the possibility of gender sensitive differences (see discussion of susceptible populations in the US-EPA IRIS report). The staff believe a default value of 5 would be sufficient to account for human population variation and the unknown potential effects of ethanedinitrile to humans.

3.) **Route to route extrapolation (difference in route animals were exposed versus humans)**

EPA: NA

Applicant: None noted

The main study used in setting the TEL was an inhalation study so no assessment factor was added as that is the main route humans will be exposed to. However, it is important to point out that the majority of the toxicity data used in assessing the chronic or repeated dose toxicity risks from ethanedinitrile inhalation of based on the results from oral exposure studies from other surrogate cyanide compounds. Cyanide entering the body by the oral route is capable of being significantly metabolized in the liver in what is known as a “first-pass-effect”. A first-pass-effect is when a chemical is absorbed in the gut and is significantly metabolized in the liver (as all blood veins exiting the intestines first drain into the liver) leading to significantly lower systemic concentrations of the active. It is important to note that the exposure route in the Lewis study was by inhalation which immediately leads to a systemic exposure rather than one that first passes through the liver which has the highest concentration of the rhodanase detoxification enzyme. The qualitative significance of this is unknown do to no TK data in animals or humans so an element of precaution is appropriate and is part of the UF associated with the database quality as used to protect against ethanedinitrile toxicity (Category 6).

4.) LOAEL to NOAEL (extrapolation from a LOAEL when a NOAEL is not available)

EPA: NA

Applicant: None noted

The key study used in the determination of the TEL had a NOAEL so no adjustment was needed.

5.) Exposure Duration (extrapolation from a subacute or subchronic exposure to a chronic exposure)

EPA: 1

Applicant: None noted

The key study used to calculate the TEL was an inhalation study of six months in duration. Chronic toxicity studies typically consist of an exposure duration of 12 months or more, thus, the Lewis study is considered to be sub-chronic in nature. Although most risk assessment guidelines state the need for an UF of 2 to be added for calculating risk from a sub-chronic to a chronic study, it is believed to be based on the fact that most sub-chronic studies are of 90 days in exposure. The California OEHHA indicates an UF of 1 can be used for studies that have a duration that is >12% of an animal's life span. Staff note that the lifespan of a laboratory rat is circa 2 years so 12% of that is ~3 months. Based on the results of studies conducted with other cyanide compounds relative to the time to the development of adverse effects the EPA believe that most effects induced by low level exposure to ethanedinitrile would likely be observed in the context of six months. The concern over the duration being sub-chronic in nature was also captured in the Modifying Factors assessment (category 7 below). The Applicant also noted the presence of one chronic oral study that found no significant cyanide-dependent effects in rats exposed to hydrogen cyanide in the diet for 2 years at higher doses (Howard and Hanzal 1955) to also support the Lewis study. However, the reliability of this study is considered very low based on the age of the study and the minimal documentation associated with the manuscript. It is noted that evaporation of the cyanide from the feed resulted in unstable cyanide levels throughout the experiment and uncertainties as to the dose-response for cyanide. In addition, this study used an oral exposure route and there are several other oral exposure studies conducted on cyanide that are much more robust that would be more appropriate. This study would also require an UF adjustment for route-to-route extrapolation concerns.

6.) **Database Quality (Completeness and consistency of the data, reliability of alternative data, e.g. read across)**

EPA: 2

Applicant: None noted

Although there is a very large and extensive data base on systemic cyanide toxicity that can be used in the qualitative assessment of the systemic toxicity potential of ethanedinitrile gas there is only one repeated dose toxicity study available to quantitatively assess its hazard potential. Furthermore, it is important to point out that the vast majority of the studies assessing cyanide toxicity were conducted using oral (water or dietary) exposures. Thus, the data base available to assess other toxicity endpoints is reliant on read-across oral studies as opposed to inhalation. The utilization of these data in the absence of TK information on ethanedinitrile is a concern that needs to be accounted for.

7.) **Modifying Factor (Professional assessment of the scientific uncertainties of the key study)**

EPA: 3

Applicant: None noted

The key study by Lewis utilized by the EPA and the Applicant has multiple issues associated with it that impact its reliability. First, as noted in category 5 above, it is only a subchronic study as opposed to a chronic duration. Based on the affiliation of one of the authors as being from Industrial Bio-test Laboratories (IBT), it is a concern that this study was also conducted there. IBT was one of the largest independent testing facilities in the United States. During a routine inspection by the FDA in 1976 numerous discrepancies between raw data and study reports, and gross deficiencies in study conduct were uncovered. Of the 867 non-acute studies reviewed under the audit programme, 618 were found to be invalid (OECD Manual for investigation of HPV Chemicals, Chapter 3 Data Evaluation). The problems were mainly associated with the sections conducting “non-acute” studies such as this one. Thus, there is significant concern of the overall reliability of this study. Furthermore, the results of this study are not well documented in the manuscript and it is quite shy relative to the standards utilized in a current OECD guideline study. For example, it utilized only 5 animals of a single sex (males) per 2 doses assessed instead of the recommended 20 animals of both sexes at three dose levels. In addition, a limited number of endpoints were either collected and or reported relative to clinical observations, numbers of tissues harvested, weighed and histologically

examined, serum clinical chemistries evaluated, and food intake. Part of the UF assigned is also associated with study duration.

Discussion

After completing the above evaluation, the UF value calculated by the EPA was actually 120. This value was ultimately adjusted to 100 for use in the derivation of the TEL. A 100 fold UF was still deemed to be an appropriate estimate based on this level being the “traditional” value of sufficiency to conservatively ensure safe chronic exposures. In the setting of the TEL, the EPA was also reflective of chronic cyanide exposure levels set by numerous other global regulatory authorities in determining the acceptability of the UF adjustment to ensure the calculated TEL was consistent with these organizations. Cyanide and cyanide compounds have a long established historical use in industrial and agricultural settings where contaminants may end up in air, food, and water. Accordingly, safe chronic exposure values have been previously set by other regulatory agencies for its presence in these mediums (Table 2). As can be seen in Table 2 the cyanide dose based on the TEL value established by the EPA is within a small magnitude of those set by other regulators. The EPA believe the UF value of 3000 utilized by the US EPA in their setting of RfC/RfD values were overly conservative as it was based on the maximal default value for each category of concern and did not account for the whole realm of toxicology data available on cyanides. The US EPA value is also inconsistent with their drinking water MCL and other globally established levels.

In addition to the questioning of the UF the EPA utilized, the Applicant also suggested that the EPA should have used the results from cyanogen exposure to primates whose results were also reported in the Lewis manuscript. The rationale being Rhesus monkeys are physiologically more similar to humans and are known to be more sensitive to cyanides than humans (NCR 2001). The EPA believes the NRC reference to “increased sensitivity” is also associated with acute toxicity and that this increased “sensitivity”, which is also associated with rodents, is simply based on the fact that these species breathe in more air per kg body weight then humans. Thus, when exposed to the same concentration of toxicant in air these species are exposed to a higher mg/kg dose. The EPA believe this physiological difference makes these species more “susceptible” to its acute toxic potential rather than being more “sensitive”. The EPA took this phenomenon into account when developing our TEL by first converting the atmospheric exposure level to the rodent into a mg/kg bw/day dose. Furthermore, staff believe that the rodent study was the more pertinent study to utilise in our

TEL calculation as there was no adverse effects noted in the primate study; whereas a significant (~13%) decrease in body weight of an unknown etiological basis (thus deemed adverse by the EPA) was seen in rats that would be suggestive to rodents being more sensitive than primates. Risk assessment guidelines stipulate that the most sensitive endpoint of toxicity should be utilised.

Conclusion

The EPA believe that the UF of 100 utilised in the calculation of the TEL was not overly conservative as asserted by the Applicant and was derived using a pragmatic approach consistent with the toxicological standards utilized by other regulatory bodies. This is made evident as the resultant estimated safe exposure limit value set by our 100 fold factor resulted in an exposure level (mg/kg) to cyanide that was similar to other globally recognized chronic exposure levels (Table 2).

The type of toxicity manifested from chronic exposure is different than that from an acute exposure, therefore, the basis for and magnitude of the UF used by the EPA for chronic exposure are different and more pertinent than those put forth by the Applicant whose UF values were based on setting safe acute exposure levels that do not need to account for all the factors the EPA used in establishing a 100 fold safety margin. Finally, the Applicant did not put forth any new scientific toxicology data in regard to the effects of cyanide that would indicate that the chronic cyanide exposure levels currently established by other regulators should be greatly increased as they have proposed.

Table 1. Default Assessment Factors Used by Various Authorities in Setting Chronic Exposure Values

		REACH TGD[1]	ECETOC[1,2]	Health Canada[3]	WHO/IPCS[2,4]	RIVM[2]	Calif.[5] (OEHHA)	US-ATSDR[3] (MRL - CN)	US-EPA[2,3] (RfC / RfD - CN)	NZ-EPA[1-4] (EDN)	Applicant[6] (EDN)
Interspecies	Uncertainties in the extrapolation of animal data to humans [toxicokinetic (TK) and toxicodynamic (TD) uncertainties)	4 (rat to human metabolic) 2.5 (remaining differences)	4	1 - 10	10 (4 x 2.5)	10	1 (human data) √10 (primate data) 10 (non primates and no TK or TD data)	10 10	10 (3.16 x 3.16) RfC 1 (human epidemiology study) RfD 10	1 – 10 4	2
Intraspecies	Variation within humans (TK and TD uncertainties)	5 (worker) 10 (general population)	3 5	1 - 10	10 (3.16 x 3.16)	3 10	1 (human data) - 10 (to allow for diversity, including infants and children, with no human TK data)	10 10	10 RfC/RfD - 10	1 – 10 5	3

		REACH TGD	ECETOC	Health Canada	WHO/IPCS	RIVM	Calif. (OEHHA)	US-ATSDR (MRL - CN)	US-EPA (RfC / RfD - CN)	NZ-EPA (EDN)	Applicant (EDN)
Route-to-route extrapolation	Oral to inhalation Inhalation to oral	2 1	(no proposal)				NA			NA	None noted
LOAEL to NOAEL		≥1 3 (majority) – 10 (exceptional)	3			10	10	10	1 - 10 10	1 – 10 (NA)	None noted
Exposure duration	Sub-chronic to chronic	2	2			10	1 (>12% of lifetime) √10 (8 - 12% of lifetime) 10 (<8% of lifetime)	NA (The MRL was developed for a specific exposure duration)	2 - 10 RfC - 3 RfD - 10	2 – 10 1	None noted

		REACH TGD	ECETOC	Health Canada	WHO/IPCS	RIVM	Calif. (OEHHA)	US-ATSDR (MRL - CN)	US-EPA (RfC / RfD - CN)	NZ-EPA (EDN)	Applicant (EDN)
Database quality	Completeness and consistency of the data, reliability of alternative data (e.g. read across)	≥1	None listed	1 - 100	1 - 10	NA	1 - √10	NA	1 - 10 RfC - 10 RfD - 3	2 – 10 2	None noted
Modifying factor	Professional assessment of the scientific uncertainties of the key study (eg. Number of animals tested)			1 - 10	1 - 10	NA		NA	1 – 10 NA	1 - 10 3	None noted
Total								100 (Exposure duration 15 – 365 days)	3000	120	6

1.) Guidance on Assessment Factors to Derive a DNEL; Technical Report No. 110 (October 2010)

2.) Dourson, M. *et al.* (1996). Evolution of science-based uncertainty factors in non-cancer risk assessment. *Regul Toxicol Pharmacol*; Oct;24(2 Pt 1):108-120.

3.) Falk-Filipsson, A. *et al.* (2007). Assessment Factors—Applications in Health Risk Assessment of Chemicals. Environ Res., 104: 108–127

4.) New Zealand Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001 (SR 2001/117) (Revoked regulations which helped defined our procedure.)

5.) Office of Environmental Health Hazard Assessment (OEHHA, 2008). Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxic Hot Spots, Risk Assessment Guidelines.

6.) National Research Council (2001). Acute Exposure Guidelines for Selected Airborne Chemicals, Hydrogen cyanide (Volume 2)

Table 2. Chronic Cyanide Exposure Values Established by Other Agencies[1]

Daily Cyanide Exposure (mg/kg bw/day)	Uncertainty Factors Applied	Agency	Exposure Source
0.0002 (0.0083 ppm)	3000	US-EPA IRIS review: Toxicological Review of Hydrogen Cyanide and Cyanide Salts, 2010	RfC – Inhalation intake
0.0006	3000	US-EPA IRIS review: Toxicological Review of Hydrogen Cyanide and Cyanide Salts, 2010	RfD – oral intake
0.0014	Not available	UK	PCV – Drinking water
0.002	100	NZ and Australia Drinking Water Standards https://www.nhmrc.gov.au/_files_nhmrc/file/nhmrc_adwg_6_-_version_3.5_-_proof_3_0.pdf	Drinking water
0.006	Not available	US-EPA	MCL – Drinking water
0.01 (0.036 ppm EDN in air)	100	New Zealand EPA (proposed)	TEL - Inhalation
0.012	100	WHO http://www.who.int/water_sanitation_health/dwq/cyanide.pdf	TDI – Food/Water
0.02	100	Council of Europe https://cot.food.gov.uk/sites/default/files/cot/cotstatementapricot200615.pdf	TDI - Food
0.05	100	US-ATDSR Agency for Toxic Substances and Disease Registry (ATSDR) (2006). US Department of Health and Human Services (2006). Toxicological profile for cyanide	MRL (15 -365 days)
0.17 (0.56 ppm EDN in air)	6	Draslovka's response to the EPA in support of our application to register EDN for use in the fumigation of export log products. 8/20/2018.	TEL (Proposed)

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- International Programme on Chemical Safety (IPCS) Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits, Environmental Health Criteria 170, 1994. http://www.inchem.org/documents/ehc/ehc/ehc170.htm

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- New Zealand Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001 (SR 2001/117).

- OECD Manual for Investigation of HPV Chemicals, Chapter 3: Data Evaluation.

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