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MEMORANDUM

To:	George Crouse, Syngenta Crop Protection
From:	Judi Durda Kathleen Neuber, Ph.D.
Date:	January 25, 2008
Subject:	Response to Comments by Nevada Division of Environmental Protection on *Toxicological Profiles for Three Organic Acids*; Phthalic Acid
Project No.:	C289

The Nevada Department of Environmental Protection (NDEP) has reviewed the subject report prepared by Integral that developed toxicological profiles for three organic acids that have been identified as site related chemicals (SRCs) at the Henderson, Nevada site. This memorandum provides our response to one of NDEP's comments regarding the toxicity value we recommended for phthalic acid, and makes a final recommendation regarding the most appropriate toxicity value for the phthalic acid that is present as an SRC at the Henderson site.

ISSUES OVERVIEW

In a letter dated January 18, 2008, NDEP questioned the basis for the toxicity criterion that we developed for phthalic acid. In our report, we derived a toxicity number for phthalic acid that was based on toxicological data for phthalic anhydride, which we regarded as an appropriate toxicological surrogate for phthalic acid (Integral 2007). In its comment letter, NDEP noted that the U.S. Environmental Protection Agency (USEPA) had developed a sub-chronic and chronic oral reference dose (RfD) for p-phthalic acid, one of three isomeric forms of phthalic acid, and questioned why this value was not used as the basis for the toxicity value we proposed for phthalic acid. Though we did not identify this USEPA-recommended toxicity value during our initial data review for this project, we have now obtained and conducted a review of the toxicological basis for USEPA's number for p-phthalic acid.

There are three isomers of phthalic acid: o-phthalic acid (known as phthalic acid), m-phthalic acid (known as isophthalic acid) and p-phthalic acid (known as terephthalic acid). The chemical of interest at the Henderson site and the one for which our toxicological profile was prepared is the o-isomer of phthalic acid.

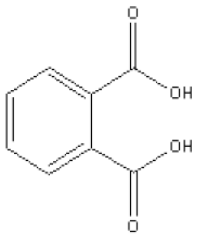
USEPA (1997) indicates that data are inadequate for quantitative risk assessment for both phthalic acid (o-phthalic acid) and isophthalic acid (m-phthalic acid). As indicated in the comment by NDEP, however, USEPA (1997) has developed an oral chronic RfD of 1 mg/kg-day for terephthalic acid (p-phthalic acid). The chronic (and subchronic) oral RfD for terephthalic acid was based upon a dietary study in rats where the critical effect was bladder hyperplasia (USEPA 1997).

In our toxicological profile report, we selected phthalic anhydride as a toxicological surrogate for phthalic acid. We did this because no long-term toxicological studies were available for phthalic acid (i.e., o-phthalic acid) and because phthalic anhydride is converted to phthalic acid when ingested. Thus, phthalic acid is the toxicologically active form of phthalic anhydride *in vivo*. USEPA (2007) has developed a chronic oral RfD for phthalic anhydride of 2 mg/kg-day based upon a dietary study in mice where the critical effects were lung and kidney histopathology. Bladder hyperplasia effects were not found in the test animals exposed to phthalic anhydride.

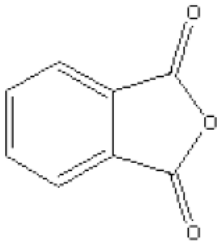
In response to the comment by NDEP, we re-evaluated both terephthalic acid (p-phthalic acid) and phthalic anhydride as potential toxicological surrogates for the form of phthalic acid (o-phthalic acid) present at the site. The results of our evaluation are presented below.

CHEMICAL IDENTIFICATION

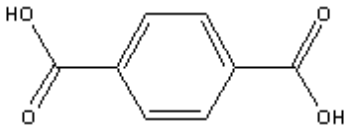
Figure 1 shows the chemical structures, formulas, molecular weight and Chemical Abstract Service (CAS) numbers for phthalic acid and the two potential surrogates: phthalic anhydride and terephthalic acid. All three of these chemicals have similar industrial uses. Phthalic acid is primarily an unisolated intermediate in the synthesis of phthalic anhydride. Phthalic anhydride is the commercial form of phthalic acid and is primarily used in plasticizers of which di-(2-ethylhexyl)phthalate is the largest. The majority of terephthalic acid produced is used in polyester fibers (USEPA 1986).



Phthalic Acid
(o-phthalic acid)
CAS No.: 88-99-3
Formula: $C_8H_6O_4$
Molecular Weight: 166.13



Phthalic Anhydride
CAS No.: 85-44-9
Formula: $C_8H_4O_3$
Molecular Weight: 148.12



Terephthalic Acid
(p-phthalic acid)
CAS No.: 100-21-0
Formula: $C_8H_6O_4$
Molecular Weight: 166.13

Figure 1. Chemical Identification: Phthalic Acid and Potential Surrogates (data from Chemfinder 2007).

Table 1 presents a brief summary of chemical and physical properties for phthalic acid and the two potential surrogates. As can be seen in Table 1, the water solubility values for phthalic acid and phthalic anhydride are similar, while the water solubility of terephthalic acid is two orders of magnitude lower. This difference has important implications for the toxicokinetics of terephthalic acid as discussed later in this memorandum.

Table 1. Physical and Chemical Properties of Phthalic Acid and Potential Surrogates.

Chemical	Phthalic acid	Phthalic anhydride	Terephthalic acid
CAS No.	88-99-3	85-44-9	100-21-0
Melting point, °C	211	131	427
Boiling point, °C	Decomposes	284	Sublimes
Water solubility (mg/L) @ 25 °C	7000	6200	19
Log K_{ow}	0.73	1.6	2

Sources: USEPA (1986); OECD (2005); Chemfinder (2007).

CHRONIC TOXICITY OF TEREPHTHALIC ACID

There are several toxicity studies available regarding the chronic toxicity of terephthalic acid in laboratory animals. Available chronic toxicity studies for terephthalic acid indicate that adverse effects observed in rats are almost completely restricted to the

urinary tract. These effects include formation of bladder calculi, and inflammatory changes and hyperplasia of the bladder epithelium (USEPA 1986, OECD 2001).

Toxicological evidence suggests that sedimentation in the urine and the formation of calculi injure the bladder epithelium and induce cell proliferation, which is probably a critical factor in the induction of bladder tumors (Heck and Tyl 1985; OECD 2001; Dai et al. 2005). Bladder calculi cannot occur unless urine becomes saturated with calcium-terephthalate. It has been estimated that the amount of terephthalic acid that would have to be absorbed by an adult human to produce the minimum saturating concentration of terephthalic acid would be 2400 mg/day (OECD 2001). Terephthalic acid is not considered to be a reproductive toxicant or to be genotoxic (OECD 2001).

The RfD of 1 mg/kg-day developed by USEPA (and identified by NDEP) for terephthalic acid presented in the Health Effects Assessment Summary Tables (HEAST) was based upon two chronic toxicity studies that identified adverse effects to the bladder in rats (Gross 1974 and CIIT 1983; as cited in USEPA 1986). The RfD was based upon a no–observed-effects level (NOEL) of 142 mg/kg-day obtained from a 2-year dietary study of two strains of rat (CIIT 1983, as cited in USEPA 1986). The NOEL was divided by applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect sensitive subgroups in the human population) to obtain the RfD.

TOXICOKINETICS

The difference in the water solubility between phthalic acid and terephthalic acid indicates that these two chemicals will very likely be absorbed, distributed, and excreted differently in mammalian systems. All three chemicals are rapidly and widely distributed and rapidly eliminated from tissues in laboratory animals (USEPA 1986, OECD 2005). Phthalic acid and terephthalic acid are both excreted unmetabolized in urine and feces (USEPA 1986). Phthalic anhydride undergoes rapid hydrolysis to phthalic acid and is excreted as phthalic acid (OECD 2005). Data are available on the excretion of both phthalic acid and terephthalic acid in rats and are summarized in Table 2. Both phthalic acid and terephthalic acid were found to be completely excreted within 24 to 48 hours of oral administration (USEPA 1986).

Table 2. Excretion of Phthalic Acid and Potential Surrogates.

Chemical	% Excreted in urine @ 24 hours	% Excreted in feces @ 24 hours	Test Animal	Test Dose	Exposure Route	Reference
Phthalic acid	23.3	76.7	Wistar rat	40 mg/kg	Oral	Williams & Blanchfield (1974)
Phthalic acid	13	NA	Sprague-Dawley rat	500 mg/kg	Oral	Lim et al. (2007)
Terephthalic acid	93.5	3.3	Wistar rat	85 mg/kg	Oral	Hoshi and Kuretani (1967) (as cited in USEPA 1986)
Phthalic anhydride	NA	NA	---	---	---	---

Notes: NA = Not available

As shown in Table 2, studies on rats showed that almost all terephthalic acid orally administered was excreted in the urine (94 percent), while very little phthalic acid was excreted in the urine (13 to 23 percent). Because the toxicological endpoint for terephthalic acid (and the basis for the USEPA RfD) is toxicity to the urinary system due to lesions caused by super-saturation of the urine with calcium-terephthalate, this difference in urinary excretion is a significant factor in the selection of a toxicological surrogate. Given the comparatively small amounts of phthalic acid that are excreted in the urine, and the relatively large saturating levels of calcium-terephthalate required to elicit toxicity, it is unlikely that adverse effects to the bladder would be associated with phthalic acid exposure. Since the RfD for terephthalic acid is entirely based upon the bladder effects as a toxicological endpoint, the dose response relationship for terephthalic acid is not relevant to phthalic acid, which is the SRC present at the Henderson site.

RECOMMENDATIONS

We recommend that the toxicity value we derived initially in our report for phthalic acid (based on phthalic anhydride) be retained as the toxicity value for use at the Henderson site. There are significant physical and chemical differences between phthalic acid and terephthalic acid. The much higher water solubility of phthalic acid and the fact that most phthalic acid is excreted through the feces, rather than the urine, suggest that the adverse effects on the bladder seen with oral exposure to terephthalic acid are not likely to occur as a result of oral exposure to phthalic acid. Conversely, toxicity data for oral exposure to

phthalic anhydride appear to be directly relevant to the potential toxicity of phthalic acid, since phthalic anhydride undergoes rapid hydrolysis to phthalic acid *in vivo*. Therefore, it is recommended that phthalic anhydride be retained as the toxicological surrogate for phthalic acid.

REFERENCES

Chemfinder. 2007. Chemfinder.com Database & Internet Searching home page. http://chemfinder.cambridgesoft.com/. Accessed on January 24, 2008. CambridgeSoft Corporation, Cambridge, MA.

CIIT. 1983. Chronic dietary administration of terephthalic acid. Chemical Industry Institute of Technology, Research Triangle Park, NC. (not seen, as cited in USEPA 1986)

Dai, Gui-Dong; Lun-Biao Cui; Ling Song; Ren-Zhen Zhao; Jian-Feng Cheng; Mei-Xia Liu; Jian-Wei Zhou; Hang Xiao; and Xin-Ru Wang. 2005. Induction of bladder lesion by terephthalic acid and its mechanism. *Biomed. Environ. Sci.* 18: 211-219.

Gross, J. 1974. The effects of prolonged feeding of terephthalic acid (TPA) to rats. Project FG-IS-175. Agricultural Research Service, U.S. Department of Agriculture, Washington, DC. (not seen, as cited in USEPA 1986).

Heck, H.D., and R.W. Tyl. 1985. The induction of bladder stones by terephthalic acid, dimethyl terephthalate, and melamine (2,4,6-Triamino-s-triazine) and its relevance to risk assessment. *Reg Toxicol. Pharm.* 5: 294-313.

Integral Consulting Inc. 2007. Toxicological profiles for three organic acids. Prepared for Syngenta Crop Protection, Inc. Integral Consulting Inc., Annapolis, MD.

Lim, Duck Soo; Bum Soo Shin; Sun Dong Yoo; Hyung Sik Kim; Seung Jun Kwack; Mi Young Ahn; and Byung Mu Lee. 2007. Toxicokinetics of phthalic acid: the common final metabolite of phthalic acid esters in rats. *J. Toxicol. Environ. Health, Part A; Current Issues*. 70: 1344-1349.

OECD. 2001. Screening information dataset initial assessment report, terephthalic acid. Available at: http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html. Organization for Economic Co-Operation and Development, Paris, France. June.

OECD. 2005. Screening information dataset initial assessment report, phthalic anhydride. Available at: http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html. Organization for Economic Co-Operation and Development, Paris, France. April.

USEPA. 1986. Health and environmental effects profile for phthalic acids (o-, m-, p-). PB89138838. U.S. Environmental Protection Agency, Environmental Criteria and

Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH. August.

USEPA. 1997. Health effects assessment summary tables, FY-1997 Update. PB97-921199. U.S. Environmental Protection Agency, Office of Research and Development, Office of Emergency and Remedial Response, Washington, DC. July.

USEPA. 2007. Integrated Risk Information System. www.epa.gov/iris/subst/0308.htm. Accessed on May 23, 2007. U.S. Environmental Protection Agency.

Williams, D.T. and B.J. Blanchfield. 1974. Retention, excretion and metabolism of phthalic acid administered orally to the rat. *Bull. Environ. Contam. Toxicol*. 12(1): 109–112.