OxoProcess Panel Comments on the
Proposed Listing of 1-butanol under CCL 4

I. Background

Under Section 1412(b)(1)(B) of the Safe Drinking Water Act (SDWA), as amended, the U.S. Environmental Protection Agency (EPA) is required to publish every five years "a list of contaminants which, at the time of publication, are not subject to any proposed or promulgated national primary drinking water regulation, which are known or anticipated to occur in public water systems, and which may require regulation under [the SDWA]."[1] Congress made it clear that in selecting unregulated contaminants for this list, known as the CCL, EPA must "consider the [National Contaminant Occurrence Database (NCOD)] established under section [1445(g) of the SDWA]"[2] and "select contaminants that present the greatest public health concern."[3] Inclusion of a contaminant on the CCL means that the contaminant, at a later date, may become subject to an EPA determination to regulate.[4] Once listed, there is no procedure set forth in the SDWA, short of a determination not to regulate, for a contaminant's removal from the particular CCL on which it appears.[5] Once listed, the chemical may be subject to an effort to develop a primary drinking water standard or screening under the EDSP.[6] The Panel therefore has a strong interest in opposing the listing on the CCL4 as the chemical exhibits low risk to human health from environmental exposures.

II. EPA's Evaluation of 1-butanol

EPA's evaluation of 1-butanol for listing on the CCL3 is documented in the "Contaminant Information Sheets for the Final CCL 3 Chemicals" (August 2009). The evaluation of 1-butanol resulted in a "3-model Categorical Prediction" value of "L?-L", indicating that 1-butanol was on the edge of whether it should be listed. Review of the "Attribute Scores" included within the CCL3 Contaminant Information Sheet for

---

[1] 42 U.S.C. § 300g-1(b)(1)(B)(i)(I). For a contaminant to be regulated under the SDWA, EPA must make three findings: (1) the contaminant may have an adverse effect on the health of persons; (2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (3) regulation presents a meaningful opportunity for health risk reduction for persons served by public water systems. Id. § 300g- 1(b)(1)(A)(i)-(iii).

[2] *Id.* § 300g-1(b)(1)(B)(i)(I).

[3] *Id.* § 300g-1(b)(1)(C).

[4] *Id.* §§ 300g-1(b)(1)(B)(ii), (E).

[5] See 70 Fed. Reg. 9071, 9073 (Feb. 24, 2005) (a determination not to regulate a particular contaminant serves to "remove that contaminant from the CCL"); but see 63 Fed. Reg. 10273, 10275 (Mar. 2, 1998) (stating that EPA is "not precluded from modifying the CCL prior to the due date of the next CCL").

[6] *See* SDWA § 1457.

1-butanol included a score of "4" (out of 10) for "Potency", "5" (out of 9) for "Severity" and "10" (out of 10) for "Prevalence" and "Magnitude". The following explains the basis for the ratings:

- The assignment of a score of "4" for potency suggests that low doses of 1-butanol do not pose a risk for human health. This conclusion is supported not only by the 1986 IRIS document providing the RfD of 0.1 mg/kg-d as referenced in the CCL 3 Contaminant Information Sheet but also the more recent evaluation by the OECD SIDS documents from 2005.

- The rating of "5" for severity is likely related to a misclassification within the 1-butanol CCL3 Contaminant Information Sheet as a "teratogen", since the effect considered for determination of the RfD was acute neurotoxic effects of hypoactivity and ataxia following oral gavage dosing of 500 mg/kg/day in a 90-day subchronic study.

- The ratings of "10" for prevalence and magnitude may be appropriate since 1-butanol is a natural component of fruits and vegetables and is ubiquitous within the environment as a product of the natural fermentation and breakdown of plants and plant products. The EPA's 2004 Toxic Release Inventory (TRI) report stating 22,011 pounds of 1-butanol was released to surface water (as noted in the CCL3 sheet) is a nominal amount compared to naturally-occurring amounts present within the environment from natural sources. Within surface water, 1-butanol biodegrades "fast" as would be expected for a naturally-occurring chemical continuously being produced and degraded within the environment.

A. Evidence that 1-Butanol is not a Toxicant of Public Health Concern

In the 1986 EPA IRIS document for 1-butanol, the RfD value was derived from a subchronic oral gavage study, (TRL, 1985), in which hypoactivity (maximum of 29% of the rats affected) and ataxia (maximum of 32% of the rats affected) were noted as acute neurotoxicity in the 500 mg/kg/day animals starting on study day 44. The onset of these symptoms was reported to occur 2-3 minutes after dosing and lasting less than one hour in duration. Questions have arisen as to why these clinical signs were not noted within this study until study day 44.

Close inspection of the study report reveals that the onset of these clinical observations occurred immediately after the number of animals/group was reduced from 30 rats/sex/group to 20 rats/sex/group due to sacrifice of 10 rats/sex/group at interim sacrifice on days 42 and 43. The study design and conduct indicated that the technical staff would administer the test articles to all of the animals, starting with the Control group and dosing the low, mid and high dose groups sequentially. This allows the technical staff to keep track of the animals and prevents administering an incorrect dose to the animals. Once all of the animals are dosed, then the technical staff goes back through the animals, in the same order, to collect post-dose clinical signs. The onset of the clinical observations of hypoactivity and ataxia immediately after the reduction in the number of animals requiring dose administration suggests that technical staff were able to complete the dosing regimen faster thereby allowing for observation of the high dose animals in a shorter period of time.

The acute onset and short duration of the clinical signs suggest that what was being noted was an example of the acute neurotoxicity of a short-chain alcohol rather than an example of cumulative toxicity of the chemical. Using an acute neurotoxic behavioral effect as the basis for a chronic RfD in an

IRIS assessment is problematic and using an UF of 1000 for a minor transient effect is unwarranted, particularly for a well-understood behavioral effect from a short chain alcohol.

A relevant comparison for the assessment of n-butanol would be to conduct a similar exercise with another short-chain alcohol, e.g. ethanol. The acute sedative effects of ethanol are well understood in both laboratory animals as well as humans. If the amount of ethanol that caused acute sedative effects in 29-32% of rats was then divided by an uncertainty factor (UF) of 1000 to arrive at an RfD, the level of concern would be so low that consumption of products that naturally contain very low concentrations of ethanol (e.g. apple juice, orange juice, vanilla ice cream) would result in exposures above the RfD for ethanol and therefore be exposures of concern. Obviously, we are not concerned with these very low exposures because we understand the dose-response relationship for these short chain alcohols. This same understanding should be applied to n-butanol in this instance and we can then recognize that the toxicity profile for n-butanol does not justify inclusion on the CCL4 listing.

B. Evidence that 1-Butanol is not a Teratogen

The 1-butanol CCL3 Contaminant Information Sheet provides a classification for 1-butanol as a "teratogen" using a reference "UMD". Since nowhere within the CCL3 contaminant list is "UMD" described, a Google search was performed and several references within the EPA describe "UMD" as "University of Maryland". It is our understanding that the Industrial Hygiene section of this university put together a non-peer reviewed list of reproductive toxins in 1995, and the EPA uses this list as a credible source of reproductive toxins. A call placed to the section within the university indicated that this list no longer exists.

More recent evaluations of the potential of 1-butanol to cause developmental toxicity (including teratogenicity) include the OECD SIDS Assessment documents that were finalized in 2005. In addition, a developmental toxicity study was conducted with 1-butanol and published (Ema, et al., 2005) that tried to replicate a previous study published in 1994 (Sitarek, et al., 1994) that was recognized to have significant methodological and reporting deficiencies. The Sitarek et al., 1994 publication was evaluated by the OECD SIDS Member States and given a Klimisch score of "3" (not reliable) within the OECD SIDS process.

Therefore, the two reliable studies available to evaluate the developmental toxicity of 1-butanol are an inhalation study by Nelson, et al., (1989) and the oral drinking water study of Ema et al., (2005). The NOAEL for both maternal and fetal effects in the Nelson study was 3500 ppm and the developmental effects (slight reductions in fetal body weight) observed at the 6000 and 8000 ppm dose levels occurred in the presence of significant maternal toxicity (narcosis, death and reductions in feed consumption). In the oral drinking water study by Ema (2005), the NOAEL for both maternal and fetal effects was 1454 mg/kg/day. Developmental effects (reductions in fetal body weight, reduced ossification and increase in skeletal variants) noted at the 5654 mg/kg/day dose level in the presence of significant maternal toxicity (decrements in feed and water consumption, reduced maternal body weight gain).

As noted by the authors of these two studies and recognized by the OECD Members States within the SIDS Process, 1-butanol causes slight developmental effects only at dose levels causing significant maternal toxicity. In addition, the NOAEL levels for either maternal or fetal toxicity are very high whether the 1-butanol is administered by inhalation or within the drinking water.

Supporting evidence that 1-butanol is not a teratogen can be found in studies conducted with n-butyl acetate. N-Butyl acetate is the acetate ester of 1-butanol and rapidly hydrolyses ($T_{1/2}$ = 22 seconds) to 1-butanol within the body. Furthermore, two publications are available that describe a physiologically-based pharmacokinetic model (PBPK model) that can be used to provide a quantitative relationship between n-butyl acetate and 1-butanol exposures (Barton, et al., 2000 and Teeguarden, et al., 2005). Developmental toxicity studies conducted with n-butyl acetate include Hackett, et al., 1982 and Saillenfait, et al., 2007. Both of these studies document that n-butyl acetate is not a developmental toxicant.

There may be other reasons why the "UMD" list included 1-butanol as a "teratogen". The database "REPROTEXT©" had for many years included 1-butanol as a "Class A- (unconfirmed human reproductive hazard)". For example, the 2010 Summary Section of the REPROTEXT® assessment of butanol contains the following statement: "A) 1-butanol has been mentioned, with other chemicals, as being possibly associated with congenital defects of the CNS in the offspring of occupationally exposed mothers (Holmberg & Nurminen, 1980; Holmberg, 1979)." However, the only mention of butanol in these references was for exposure to the "referent" (control) population of mothers that had healthy babies and who were compared to the case control population of exposed mothers. There is no mention in either of the cited publications associating 1-butanol with congenital defects of the CNS in the offspring of occupationally exposed mothers. The below table is from the Holmberg & Nurminen, 1980; Holmberg, 1979 studies:

Exposure at Work of 12 Case Mothers Containing Diagnosis of Child's Malformation, Respectively, and of Three Referent Mothers of Healthy Children[7]

Type of exposure	**Solvents**	**CNS Defect**
Case		
plastics manufacturing	styrene; acetone	hydrocephaly
leather industry	denatured alcohol + dyes	anencephaly
textile industry	ethylene oxide; alkylphenol + dyes	hydrocephaly
community service (laboratory)	benzene; dichloromethane; methanol; ether	anencephaly
cultural services (museum)	white spirit[a]	hydrocephaly
plastics manufacturing	styrene; acetone	anencephaly
printing and publishing	white spirit	meningomyelocele with hydrocephaly
rubber products manufacturing	toluene; xylene; white spirit; methylethylketone	hydranencephaly
metal products manufacturing	petrol; denatured alcohol	meningocele
metal products manufacturing	toluene	internal congenital hydrocephaly; agenesis of corpus callosum

[7] Table extracted from Holmberg & Nurminen, 1980; Holmberg, 1979, emphasis added.

leather industry	denatured alcohol + dyes	hydrocephaly
building	toluene, white spirit	meningomyelocele

Referent

equipment manufacturing	xylene, **butanol**
community services (laboratory)	mixed aromatic/aliphatic
community services (surgery)	halothane, ether

The "REPROTEXT©" database was contacted once this error was noticed and after several years, the database was corrected in April of 2013. Currently, the "REPROTEXT©" database rates 1-butanol as a "B-" (few reproductive effects in animals but no human data). The reproductive effects the database is referring to are the developmental effects (reduced fetal body weight and decreased ossification) noted at the dose levels causing significant maternal toxicity.

For the reasons noted above, the Oxo Process Panel believes the designation of "teratogen" contained within the CCL3 Contaminant Information Sheet is incorrect. The designation of "teratogen" from the "Other Supporting Data" section of the 1-butanol summary sheet should be removed.

C. 1-butanol is not a Drinking Water Contaminant

1-butanol has a distinct rancid odor that is very disagreeable to those encounter it. In fact, laboratories that explore the sense of smell and evaluate anosmics (people who have lost the sense of smell) use 1-butanol as a positive control agent. The median odor threshold for 1-butanol in a well-controlled study was 0.17 ppm (Wysocki and Dalton, 1996). These facts are relevant as any contamination of drinking water with 1-butanol would result in an odor that would affect the potability of the water source. In other words, if a water source was contaminated with 1-butanol, it would not be consumed by the human population because the odor is so foul. As such, EPA's finding that there was no reported drinking water contamination with 1-butanol (as reported in the CCL 3 Contaminant Sheet) is not because the chemical could not be detected. Rather, there simply is little to no contamination of drinking water supplies by 1-butanol.

In conclusion, because evidence does not support 1-butanol as a teratogen and is not a drinking water contaminant, the Oxo Process Panel requests that 1-butanol be removed from the CCL4 list due to the low risk to human health from environmental exposures to 1-butanol.

REFERENCES

Barton, HA, Deisinger, PJ, English, JC, Gearhart, JM, Faber, WD, Tyler, TR, Banton, MI, Teeguarden, J, and ME, Andersen. (2000) "Family Approach for Estimating Reference Concentrations/Doses for Series of Related Organic Chemicals". Toxicol. Sci. 54, 251-261.

Ema, M, Hara, H, Matsumoto, M, Hirose, A, and E, Kamata (2005) "Evaluation of the developmental toxicity of 1-butanol given to rats in drinking water throughout pregnancy" Food Chem. Toxicol. Feb; 43(2):325-331.

Hackett, PL, Brown, MG, Buschbom, RL, Clark, ML, Miller, RA, Music, RL, Rowe, SE, Schirmer, RE, and MR Sikov. 1982. Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl Acetate. Prepared by the U.S. Department of Health and Human Services. Public Health Service. Center for Disease Control. National Institute for Occupational Safety and Health. Department of Biomedical and Behavioral Science. Experimental Toxicology Branch. Cincinnati, Ohio 45266. NTIS PB83-258038.

Holmberg, PC, (1979) "Central Nervous System in Children born to Mothers Exposed to Organic Solvents During Pregnancy" Lancet 2:177-179.

Holmberg, PC, and M, Nurminen. (1980) "Congenital Defects of the Central Nervous System and Occupational Factors during Pregnancy. A Case-Referent Study" Am J Ind Med 1:167-176.

Nelson, BK, Brightwell, WS, Kahn, A, Burg, JR, and PT, Goad. (1989) "Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats". Fundamental and Applied Toxicology. 12(3):469-479.

OECD SIDS Program 2005 review of 1-butanol. Retrieved from http://www.chem.unep.ch/irptc/sids/OECDSIDS/71363.pdf

REPROTEXT® database. Accessed November 2010.

Saillenfait, A-M, Gallissot,F, Sabate, J-P, Bourges-Abella, N, and S, Muller (2007) "Developmental toxic effects of ethylbenzene or toluene alone or in combination with butyl acetate in rats after inhalation exposure" J. Applied Toxicol. 27:32-42.

Sitarek, K, Berlinska, B, and B. Baranski. (1994) "Assessment of the Effect of 1-butanol Given to Female Rats in Drinking Water on Fertility and Prenatal Development of Their Offspring". Int. J. of Occupational Medicine and Environmental Health, 7(4):365-370.

Teeguarden, J.G., P. J. Deisinger, T.S. Poet, J. C. English, W.D. Faber, H.A. Barton, R.A. Corley, and H. J. Clewell III (2005) "Derivation of a Human Equivalent Concentration for 1-butanol Using A Physiologically-Based Pharmacokinetic Model for n-Butyl Acetate and Metabolites 1-butanol and n-Butyric Acid" Tox. Sci., 85:429-446.

TRL. (1986) Rat Oral Subchronic Toxicity Study of Normal Butanol Toxicity Research Laboratories, Ltd. Muskegon, MI. TRL Study #032-006 dated 1986

Wysocki, C.J. and Dalton, P. (1996). "Odor and Irritation Thresholds for 1-Butanol in Humans." Monell Chemical Senses Center. Philadelphia, PA.