Response to EPA's Hazard Characterization of the Aromatic Extracts Category

The American Petroleum Institute Petroleum HPV Testing Group

June 17, 2013

The following comments are in response to EPA's Hazard Characterization (HC) for the Aromatic Extracts Category (U.S. EPA, 2012). This Category was sponsored by the American Petroleum Institute (API) Petroleum HPV Testing Group (Testing Group) as part of EPA's HPV Chemical Challenge Program (www.petroleumhpv.org).

Below is EPA's generic table of content for all the HPV Hazard Characterizations they have prepared, including Aromatic Extracts. The Testing Group's comments are found on the page numbers indicated below.

Summary

1. The EPA hazard characterization for several Petroleum HPV Categories including Aromatic Extracts, refers to the category members as complex mixtures when in fact they are Class 2 UVCB substances. (HC pages 5, 9, 11, 13, 33, and Table 1)

Substances on the US TSCA Inventory are divided into two classes for ease of identification (EPA 1995). Class 1 substances are those single compounds composed of molecules with particular atoms arranged in a definite, known structure. However, many commercial substances that are subject to TSCA are not Class 1 substances, because they have unknown or variable compositions or are composed of a complex combination of different molecules. These are designated Class 2 substances. Class 2 includes substances that have no definite molecular formula representation and either partial structural diagrams or no structural diagrams. These are the "UVCB" substances (Unknown or Variable compositions, Complex reaction products and Biological materials). An example of this kind of substance is given below.

CAS Number: 64742-04-7
CAS Name: Extracts (Petroleum), Heavy Paraffinic Distillate Solvent
CAS Definition: A complex combination of hydrocarbons obtained as the extract from a solvent extraction process. It consists predominantly of aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C50. This stream is likely to contain 5 wt. % or more of 4- to 6-membered condensed ring aromatic hydrocarbons.

Petroleum substances are subject to nomenclature rules developed jointly by the U.S. EPA and the American Petroleum Institute (EPA, 1995b). In that guidance document, EPA adopts the definitions of petroleum process stream terms provided in API's published reference document Petroleum Stream Terms Included in the Chemical Substance Inventory under TSCA (1983, reprinted in 1985). The Stream Terms definitions include the CAS definition and registry number, the source of the substance and process (i.e., last refining step), short name, indication of carbon number, and indication of distillation range (or other appropriate characteristic). Therefore all members of the Aromatic Extracts Category are UVCB substances, not mixtures, under EPA's nomenclature guidance.

3. Human Health Hazard

The key reason for the data "gaps" identified by EPA for this Category is the organization of the 5 substances into subcategories. EPA treated subcategories as barriers that don't allow read-across of mammalian data between them. The Testing Group believes the Aromatic Extracts Category is better described as a continuum of similar substances and the human health hazards of this category are associated with the presence of polycyclic aromatic compounds (PACs) in the substance. This knowledge coupled with existing and new testing data should satisfy all the HPV requirements for human health data.

The Testing Group described a modeling approach for assessing the repeat-dose, developmental, and gentox endpoints of substances in this Category. However, EPA did not acknowledge the utility of the statistical models used in the category assessment document submitted by the Testing Group. In the original Test Plan for Aromatic Extracts, a relationship between mammalian toxicity and the polycyclic aromatic compound (PAC) content of the

substances in that category was asserted or implied. To study this relationship, toxicology studies and analytical reports on high-boiling petroleum substances (HBPS) like aromatic extracts were collected from the Testing Group's member companies and analyzed in order to address two key questions: 1) Are there quantitative relationships between PAC content of petroleum substances and their critical effects as identified in repeat-dose, developmental, bacterial genotoxicity, and reproductive toxicity studies, and 2) can the critical effects/levels of untested petroleum substances be predicted from their PAC content?

The assessment by the Testing Group showed (a) that the toxicological effects of high boiling petroleum-derived substances (i.e., final boiling points > 650 ^{o}F) were associated with PAC content, (b) that subchronic effects associated with PAC content included liver enlargement, thymic weight reductions, reduced hematological parameters, and developmental effects including reduced live-births and birth-weight, and (c) that the effects of these high boiling petroleum-derived substances could be predicted from PAC contents using predictive statistical models for several repeat-dose and developmental toxicity endpoints. The models used the weight percent of each of the aromatic ring classes (the "PAC profile") as the independent variable. The effects found to be associated with the PAC profile are consistent with those reported for a number of individual PAHs and PAC-containing materials. A predictive model for bacterial mutagenesis was also developed. The Testing Group had the results of its model building exercise reviewed through an expert peer consultation process (TERA, 2008). The Testing Group has followed up the peer consultation with additional testing and analysis and has prepared several detailed manuscripts for publication (Murray et al., 2013; Nicolich et al., 2013; Roth et al., 2013; McKee et al., 2013).

Repeated-Dose Toxicity

EPA recommended testing on light paraffinic and light naphthenic distillate extracts including subchronic, repro/developmental, and chromosome aberrations endpoints. A sample of light naphthenic distillate extract could not be obtained but an OECD 411 repeat-dose toxicity study (WIL Research, 2012a) was done on a sample of light paraffinic distillate extract (CAS 64742-05-8). A robust summary of that study was included in the Testing Group's May 2012 submission to EPA. Because the mammalian toxicity depends on the PAC profile of the sample and can be adequately defined by statistical models developed by the Testing Group, no additional testing is needed on naphthenic distillate extracts.

Developmental Toxicity

EPA recommended testing on light paraffinic and light naphthenic distillate extracts including subchronic, repro/developmental, and chromosome aberrations endpoints. A sample of light naphthenic distillate extract could not be obtained but an OECD 414 developmental toxicity study (WIL Research, 2012b) was done on a sample of light paraffinic distillate extract (CAS 64742-05-8). A robust summary of that study was included in the Testing Group's May 2012 submission to EPA. Because the mammalian toxicity depends on the PAC profile of the sample and can be adequately defined by statistical models developed by the Testing Group, no additional testing is needed on naphthenic distillate extracts.

Genetic Toxicity – Chromosomal Aberrations

EPA recommended testing on light paraffinic and light naphthenic distillate extracts including subchronic, repro/developmental, and chromosome aberrations endpoints. A sample of light naphthenic distillate extract could not be obtained but an OECD 474 micronucleus toxicity study (WIL Research, 2012a) was done on a sample of light paraffinic distillate extract (CAS 64742-05-8). A robust summary of that study was included in the Testing Group's May 2012 submission to EPA. Because the mammalian toxicity depends on the PAC profile of the sample, no additional testing is needed on naphthenic distillate extracts.

Reproductive Toxicity

EPA identified mammalian reproductive toxicity as a data gap under the HPV Challenge Program for several Petroleum HPV Categories including Aromatic Extracts. However, the original guidance provided by EPA for fulfilling the reproductive toxicity data requirement was developed by the Organization for Economic Cooperation and Development (OECD) Guidance for Meeting the SIDS Requirements (http://www.epa.gov/HPV/pubs/general/sidsappb.htm). That guidance says that when a 90-day repeat dose study (such as OECD 408) is available and is sufficiently documented with respect to studying effects on the reproductive organs and a developmental study (such as OECD 414) is available, the requirements for the reproduction toxicity endpoint are satisfied. Other studies that satisfy the endpoint are screening-level tests defined by such guideline protocols as the OECD 421 or 422, or a one- or two-generation study defined by such guideline protocols as OECD 415 or 416. The Testing Group believes the data cited in the Category Assessment Document for Aromatic Extracts is sufficient to satisfy the SIDS requirements for reproductive toxicity.

4. Hazard to the Environment

EPA states in the summary:
"For ecotoxicity, the two subcategories are based on physical-chemical properties. Subcategory I contains light paraffinic and light naphthenic distillate, solvent extracts and Subcategory II contains heavy paraffinic and heavy naphthenic distillate, solvent extracts and residual oil, solvent extract.

- Subcategory I
  No adequate acute and chronic toxicity data are available for aquatic organism. The acute toxicity to fish and aquatic invertebrates, toxicity to aquatic plants, and chronic toxicity to aquatic invertebrates are identified as data gaps for subcategory I under the HPV Challenge Program.

- Subcategory II
  No adequate acute and chronic toxicity data are available for aquatic organism. However, based on the physical-chemical properties of the category members [log Kow (8.0 to 19.6) and water solubility (<1x10-6 to 0.002 mg/L)], acute and chronic aquatic toxicity to aquatic organisms is not expected."

EPA states in Section 4. Environmental Effects – Aquatic Toxicity:
"A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4. The submitted studies were all conducted using water accommodated fractions (WAFs) without reporting measured concentrations for the test solutions. Initially, EPA accepted the studies that

the sponsor submitted. Upon further review, EPA decided to use them as weight of evidence to support EPA's conclusions. They are included in the appendix of this document; however, there is not enough detailed information included in these studies for consideration as critical studies."

In May 2012, the Testing Group issued its Category Assessment Document (CAD) for the Aromatic Extracts category (API, 2012). Included in the Testing Group's CAD and robust summaries were two new ecotoxicity studies conducted by CONCAWE (2010a,b) on Daphnia magna and Pseudokirchneriella subcapitata using light paraffinic distillate, solvent extract (CASRN 64742-05-8).

For acute toxicity to fish, the Testing Group employed the PETROTOX model to estimate the acute lethal loading of the light paraffinic distillate solvent extract (CASRN 64742-05-8). This model employs the hydrocarbon block method (CONCAWE, 1996; Redman et al., 2012) using comprehensive 2D-GC analysis of the test sample. The input compositional matrix and model output are presented in Figure 1 (at the end of this document). The model estimated the fish acute LL50 to be >1000 mg/L loading, which is consistent with the study data presented in the Testing Group's original Test Plan and Category Analysis Document (API, 2003, 2012).

These new data satisfy the SIDS endpoints for these three species and can be used as read-across to the light naphthenic distillate, solvent extract (CASRN 64742-03-6).

EPA states that no adequate data was submitted by the Testing Group because they were based on WAF exposures. The Testing Group believes that results for multi-constituent, poorly soluble hydrocarbons should be expressed as lethal loadings (LL) rather than lethal/effect concentrations (LC, EC). Loading is a more effective means of comparing two substances to each other because the hydrocarbon composition in the WAF varies with composition of these streams. Loading is a reflection of the composition and chemistry of the substance and implicitly accounts for multicomponent dissolution and volatilization.

Aquatic toxicity of petroleum streams is attributed to the neutral organic hydrocarbon constituents whose toxic mode of action is non-polar narcosis. Hydrocarbons are equitoxic in tissues where the toxic mechanism of short-term toxicity for these chemicals is disruption of biological membrane function (van Wezel and Opperhuizen, 1995). The differences between toxicities (i.e., LC/LL5O, EC/EL50) can be explained by the differences between the target tissue-partitioning behaviors of the individual chemicals (Verbruggen et al., 2000). The existing fish toxicity database for hydrophobic neutral chemicals supports a critical body residue (CBR, the internal concentration that causes mortality) of approximately 2-8 mmol/kg fish (wet weight) (McGrath and Di Toro, 2009). When normalized to lipid content the CBR is approximately 50 µmol/g of lipid for most organisms (Di Toro et al., 2000).

When compared on the basis of standard test methods and exposure solution preparation procedures, aromatic extracts are expected to produce a similar range of toxicity for the three trophic level species. Results expressed as measured concentrations of the fraction of the substance in solution are of little value since it will be virtually impossible to extrapolate to spill situations where the only relevant measures of concentration will be the amount of product spilled and the volume of the receiving environment (i.e., the loading rates). Loading rates provide a unifying concept for expressing the results of a toxicity test with poorly-soluble substances (European Eco-Labeling Criteria; ASTM 2009; GESAMP; OECD 2006; ECHA). Preparation of independent WAFs based on test substance loading rates is the appropriate procedure for products in this category because these products are multi-constituent

hydrocarbons whose constituent hydrocarbons vary in water solubility. The dissolution thermodynamics of a multi-constituent hydrocarbon in an aqueous medium limit the likelihood of consistent proportional concentrations of the constituent hydrocarbons at various test substance loading rates. For this reason,

- exposure solutions are not prepared from dilutions of a stock solution (the relative proportion of hydrocarbon constituents in the dilutions would not accurately reflect the relative concentration of those constituent chemicals in individually prepared, successively lower exposure solutions of the test material), and
- separate exposure solutions are prepared at each exposure loading for products that are multi-constituent hydrocarbons.

When properly prepared, WAFs represent the equilibrium condition of maximally dissolved test substance for its respective loading rate. Any excess test substance is separated from the solutions used in testing, allowing the use of only dissolved constituents or those that create stable dispersions.

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Figure 1.

	Dmagna	Selen. Capri	Oncho. Mykiss
LL50	**>1000**	**>1000**	**>1000**
TU (acute)	**0.34**	**0.30**	**0.59**
LL10	**0.28**	**3.76**	**0.04**
TU (chronic)	**1.00**	**1.00**	**1.00**

Hydrocarbon Block	Starting Carbon Number	Ending Carbon Number	n-P	i-P	n-CC5	n-CC6	i-N	Di-N	n-Olefins	i-Olefins	Poly-N	AlS	MoAr	NMAr	DiAr	NDiAr	PolyAr	ArS
			(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)	(weight %)
1	5	6	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	6	7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
3	7	8	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
4	8	9	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
5	9	10	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
6	10	11	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
7	11	12	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
8	12	13	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
9	13	14	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.034	0.029	0.000
10	14	15	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
11	15	16	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000
12	16	17	0.000	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.170	0.000
13	17	18	0.001	0.000	0.026	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.018	0.000	0.000	0.699	0.000
14	18	19	0.013	0.001	0.026	0.026	0.023	0.027	0.000	0.000	0.000	0.000	0.105	0.195	0.004	0.000	2.307	0.000
15	19	20	0.082	0.026	0.026	0.026	0.116	0.148	0.000	0.000	0.000	0.000	0.536	0.556	0.091	0.009	4.721	0.000
16	20	21	0.306	0.122	0.026	0.026	0.272	0.349	0.000	0.000	0.000	0.000	1.183	1.175	0.493	0.095	7.919	0.000
17	21	22	0.588	0.297	0.026	0.026	0.578	0.517	0.000	0.000	0.000	0.000	1.859	1.687	0.995	0.580	8.263	0.000
18	22	23	0.744	0.450	0.026	0.026	0.676	0.497	0.000	0.000	0.000	0.000	1.954	1.469	1.828	1.679	9.524	0.000
19	23	24	0.696	0.698	0.026	0.026	0.516	0.502	0.000	0.000	0.000	0.000	1.574	0.911	1.541	3.189	8.614	0.000
20	24	25	0.413	0.347	0.026	0.026	0.313	0.319	0.000	0.000	0.000	0.000	0.810	0.584	0.754	3.468	4.602	0.000
21	25	26	0.177	0.340	0.026	0.026	0.171	0.177	0.000	0.000	0.000	0.000	0.442	0.259	0.429	2.337	2.116	0.000
22	26	27	0.088	0.310	0.026	0.026	0.084	0.093	0.000	0.000	0.000	0.000	0.223	0.163	0.204	1.080	0.793	0.000
23	27	28	0.041	0.187	0.026	0.026	0.021	0.060	0.000	0.000	0.000	0.000	0.108	0.095	0.099	0.584	0.533	0.000
24	28	29	0.031	0.116	0.026	0.026	0.043	0.025	0.000	0.000	0.000	0.000	0.048	0.052	0.053	0.284	0.252	0.000
25	29	30	0.021	0.062	0.026	0.026	0.011	0.020	0.000	0.000	0.000	0.000	0.024	0.034	0.029	0.133	0.127	0.000
26	30	31	0.010	0.032	0.026	0.026	0.017	0.033	0.000	0.000	0.000	0.000	0.032	0.000	0.023	0.075	0.074	0.000

Figure 1. PETROTOX 2D-GC input and model output of fish acute toxicity estimate for light paraffinic distillate, solvent extract (CASRN 64742-05-8).