Response to EPA's Hazard Characterization of the Crude Oil Category

The American Petroleum Institute Petroleum HPV Testing Group
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The following comments are in response to EPA's Hazard Characterization (HC) for the Crude Oil Category (U.S. EPA, 2011). 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 Crude Oil. The Testing Group's comments are found on the page numbers indicated below.

EPA HC Content **Testing Group Comments**

Summary

1. The Chemical Abstract Index Name is "Petroleum", not "Crude Petroleum". (HC page 3)

2. The HC describes Crude Oil as a "complex mixture" several times when in fact it is a substance, a Class 2 UVCB substance. (HC pages 3, 5, 6, 9)

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: 8002-05-9
CAS Name: Petroleum
CAS Definition: A complex combination of hydrocarbons. It consists predominantly of aliphatic, alicyclic and aromatic hydrocarbons. It may also contain small amounts of nitrogen, oxygen and sulfur compounds. This category encompasses light, medium, and heavy petroleums, as well as the oils extracted from tar sands. Hydrocarbonaceous materials requiring major chemical changes for their recovery or conversion to petroleum refinery feedstocks such as crude shale oils, upgrade shale oils and liquid coal fuels are not included in this definition.

3. Human Health Hazard

EPA did not acknowledge the utility of the statistical models used in the category assessment document submitted by the Testing Group to evaluate untested samples of crude oil. In the original Test Plan for Crude Oil, 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 Crude Oil 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, (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 the PAC content 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 (Patterson et al,, 2013). 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., 2013a). The statistical models have been applied to Crude oil samples and the results of this investigation have been accepted for publication (McKee et al., 2013b).

Reproductive Toxicity

US EPA identified mammalian reproductive toxicity as a data gap under the HPV Challenge Program for crude oil. However, US EPA provided guidance for fulfilling the reproductive toxicity data requirement under the HPV Challenge Program by adopting 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 sufficiently documented with respect to studying effects on the reproductive organs along with a developmental study (such as OECD 414) 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. Data from 408 and 414 studies on two crude oils that meet the criteria listed above have been published (Feuston et al., 1997a;b) and were summarized in the CAD submitted by the API. Thus the API believes that the endpoint has been fully characterized in accordance with HPV program requirements.

Further, the Testing Group believes that published literature provides data suitable for assessing the SIDS reproductive toxicity endpoint for crude oil for both the inhalation and dermal route of exposure. Additional toxicology testing to address the reproductive hazard of crude oil is unnecessary. The dermal hazard of crude oil is directly related to the presence of polycyclic aromatic compounds (PAC) in crude oil. The inhalation hazard of crude oil is due to possible presence of hydrogen sulfide or from volatile organic compounds (VOC) emitted from the crude oil. The relevant data for reproduction is summarized in the Testing Group's Category Assessment Document (CAD page 55 – 58) and in the table below.

Summary of Published Studies to Address Reproductive Toxicity

Route	Test Substance	OECD Study Type	Publication
Dermal	2 Crude Oils	408	Fueston et al., 1997a
Dermal	2 Crude Oils	414	Fueston et al., 1997b
Inhalation	Hydrogen Sulfide	421	Dorman et al., 2000
Inhalation	Gasoline VOCs	416	McKee et al., 2000

Genetic Toxicity - Chromosomal Aberrations

US EPA concluded that for the SIDS endpoint, *in vivo* chromosome aberrations, crude oil was considered to give a positive response (HC Table 3). The Testing Group believes that this endpoint should be considered negative. The basis for EPA's conclusion appears to be the publication by Lockard et al., 1982; however, the only "positive" result in the Lockard et al., 1982

study was for sister chromosome exchange (SCE) but the SCE test is not a measure of chromosome aberrations. The biological significance of SCEs is not known. Further, the study used very small groups of mice (3 per dose) and gave large doses of crude oil intraperitoneally. Only at the high dose of over 7 grams/kilogram body weight was there a statistically significant increase in SCEs.

On the other hand there have been several studies which did assess the potential for chromosomal aberrations, and in all of these studies negative results were obtained. The paper referenced above (Lockard et al., 1982) reported that the substance that increased the SCE incidence (Wilmington crude oil, 7.2 g/kg i.p.) did not increase the frequency of micronuclei. There are two other *in vivo* micronucleus studies with crude oil that were also negative. Rats treated dermally for 13-weeks with Lost Hills Light or Belridge Heavy crude oils at doses of 0, 30, 125 or 500 mg/kg for 13 weeks demonstrated that these crude oils did not induce cytogenetic damage in the bone marrow after repeated exposures (Mobil, 1990c; 1991e). Overall crude oil should be considered negative for *in vivo* chromosome aberrations.

Skin Irritation and Eye Irritation

US EPA indicates for eye and skin irritation that crude oil is "Positive". The data in the table below on skin and eye irritation demonstrate variability among different crude oils but suggest that overall crude oil is not corrosive or a severe irritant. EPA may wish to qualify the term "Positive" to better inform the reader of the hazard.

Summary of Skin and Eye Irritation Studies on Crude Oil[1]

Sample	**Skin Irritation (Rabbit)[2]**		**Eye Irritation (Rabbit 24hr) Conjunctival[3]**
	Erythema	**Edema**	
Beryl [36.5°API]	ND	ND	1.7
Arab Lt [34.5 °API]	0.9	0.1	1.3
Mid-Continent [40°API]	ND	ND	0.3
Lost Hills Light [>38°API]	1.6	1.3	3.7
Belridge Heavy [14°API]	0.6	0.8	0.8

[1] Mobil, 1985a,b; 1990a,b
[2] Mean scores on a scale of zero to four, reactions at 24, 48, and 72 hrs.
[3] Mean scores on a scale of zero to twenty at 24 hrs. (All Iris and Cornea scores were zero)
ND = Not Determined

Carcinogenicity

EPA reported that in the study by Perez-Cadahia et al., 2007, workers were exposed to crude oil, however, the Prestige tanker incident was a spill of heavy fuel oil which is significantly different in composition. (HC page 21). Since this incident did not involve exposure to crude oil, it should be removed from the EPA HC.

4. Hazard to the Environment

EPA did not use the lethal loading data provided by the Testing Group but instead cites the following lethal/effects concentrations for this category:
The 96-h LC50 of CASRN 8002-05-9 for fish ranges from 0.73 to 42 mg/L. The 48-h EC50 of CASRN 8002-05-9 for aquatic invertebrates ranges from 0.61 to 28 mg/L. The 21-d chronic toxicity to aquatic invertebrates ranges from 0.5 to 6 mg/L. (HC page 4, 35, and Table 4).

1. The Testing Group argues that results for petroleum UVCBs like crude oil (multi-constituent, poorly soluble hydrocarbons) should be expressed as lethal loadings (LL) rather than lethal/effect concentrations (LC, EC). The Testing Group maintains that when toxicity endpoints are more accurately expressed as 'loading rates', crude oils are expected to exhibit aquatic toxicity at approximately 1 mg/L or higher for the three trophic levels. Loading is a more effective means of comparing two substances to each other because the hydrocarbon composition in the WAF varies with composition of the crude oil. Loading is a reflection of the composition and chemistry of the substance and implicitly accounts for dissolution and volatilization of the hydrocarbon constituents.

Crude oil aquatic toxicity 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, crude oils 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 petroleum UVCBs because these substances 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 substances that are petroleum UVCBs (multi-constituent hydrocarbons).

2. Additionally the Testing Group cannot evaluate the relevancy or reliability of the effects values cited by EPA due to the lack of citations/robust summaries for cited data. EPA's HC lists 27 fish data endpoints and 35 invertebrate data endpoints (Section 4, pages 24-35). In most cases the sources of the cited data are not provided (for the 27 fish studies, 19 lack references; of the 35 invertebrate studies, 25 lack references). The one or two sentence descriptions given in the HC for each study cannot allow a determination of the quality of the work, and full robust summaries of the original journal/study reports should be provided.

3. Further reason to contest values cited by EPA in Table 4, page 35, summary of SIDS data, is that the ranges of endpoint values for fish and aquatic invertebrates are all based on unspecified measures of concentration. Additionally, not all ranges can be verified in the tests cited in the HC. For example, the range cited for chronic invertebrate toxicity is 0.5 – 6 mg/L), but there is no study citing a chronic toxicity endpoint of 6 mg/L.

Toxicity to Aquatic Plants

The toxicity of crude oil to aquatic plants (algae) was described in API's Category Assessment Document (CAD) that was submitted to EPA January 2011 (API 2011). The robust summary for the data cited in Tsvetnenko and Evans, 2002 was inadvertently omitted from the submission documents. The robust summary will be provided to EPA and together with the data from Gaur and Singh, 1989, should fill the EPA data gap for this endpoint.

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