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EPA Comments on Chemical RTK HPV Challenge Submission:Potassium 2-ethylhexanoate and Calcium bis(2-ethylhexanoate) Category

Summary of EPA Comments

The sponsor, the Metal Carboxylates Coalition, submitted a test plan and robust summaries to EPA for the revised Potassium 2-ethylhexanoate and Calcium bis(2-ethylhexanoate) category, dated June 23, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 27, 2004. The category consists of Potassium 2-ethylhexanoate (CAS No. 3164-85-0) and Calcium bis(2-ethylhexanoate)(CAS No. 136-51-6).

EPA has reviewed this submission and has reached the following conclusions:

1. General. The submitter needs to provide data or a technical discussion to support the assertion that the toxicity of the salts is equivalent to that of the separate metal ions and their respective organic acids.
Response: These metal carboxylate salts are designed to dissociate into free metal and free acid. One characteristic of these metal carboxylates is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). Dissociation is a reversible process and the proportion of dissociated salt is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for these metal carboxylates. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH. Dissociation is a reversible reaction, splitting the parent compound into two or more chemical Species which may be ionic, but are not necessarily so. The process can be generally represented as:

	PK1		PK2	
$[RCOO]_x:[M^+]$	$\Longleftrightarrow$	$[RCOO]_x + [M^+]$	$\Longleftrightarrow$	$[RCOOH]_x + [M^+]$
undissociated salt high pH		dissociated acid and metal		neutral species and ionized metal low pH

These results indicate that a moderate amount of dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at the physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the dissociation products to support the existing data for the metal carboxylate salts in the fulfillment of critical endpoints.

The dissociation constants show that at the pH of the stomach, the important moieties from a toxicological standpoint are the unionized free acid and ionized calcium/potassium. Because of this dissociation in the stomach, mammalian toxicity data for the 2-ethylhexanoic acid can serve as a surrogate data for the carboxylic acid component of the two parent compounds. Similarly, under these conditions, data for calcium and potassium can be represented by fate and toxicity data for free ion or simple metal salts (e.g., calcium chloride or potassium chloride). Calcium and potassium are not considered toxic moieties. Therefore, the role in any observed toxicity for acids and metals can be evaluated independently. The combination of the acid and the metal can be used to supplement the characterization of toxicity of the salt and support a read across as part of the category strategy to determine needs for additional data.

2. Category Definition. The category is clearly defined.
Response: Noted

3. Category Justification. The submitter's support for grouping these chemicals is reasonable.
Response: Noted

4. Physicochemical Properties. The submitter needs to provide measured melting point data and reliable water solubility data for the calcium salt, and address deficiencies in the robust summaries.
Response:

- Melting point data have been provided. Water solubility data are not available for calcium 2-EHA. Data on similar compounds, such as calcium soaps, are available. Calcium soaps (calcium stearate, calcium palmitate, and calcium abietate) are made by the action of the sodium salts of the acids on a soluble calcium salt such as calcium chloride ($CaCl_2$). Calcium soaps are insoluble in water but are soluble in hydrocarbons. They tend to form jellylike masses and are used as constituents of greases and as waterproofing agents.
- Agree. Deficiencies in the physicochemical robust summaries will be addressed.

5. Environmental Fate. EPA agrees with the submitter that no further testing is needed. However, the submitter needs to provide a technical discussion for the photodegradation endpoint. Also, a technical discussion needs to be provided for the stability in water endpoint, referencing the dissociation of the metal salt complexes. The submitter needs to address deficiencies in the robust summaries.
Response:

- Photodegradation modeling was performed for the parent substances. However, these results may not be applicable as these substances readily dissociate.
- Hydrolysis studies were not conducted as these metal carboxylate salts are designed to dissociate into free metal and free acid.
- Agree. Deficiencies in the environmental fate robust summaries will be addressed.

6. Health Effects. Adequate data were submitted for all SIDS endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.
Response: Agree. Deficiencies in the robust summaries for the calcium salt will be addressed if this information is readily available.

7. Ecological Effects. EPA reserves judgement for these endpoints until deficiencies in the robust summaries for 2-ethylhexanoic acid are addressed.
Response: Disagree. It is not the responsibility of the Metal Carboxylates Coalition to address deficiencies in the 2-ethyhexanoic acid robust study summaries since these were presented at SIAM 9 and updates of this document are the responsibility of the producers of that material.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the Potassium 2-ethylhexanoate and Calcium Bis(2-ethylhexanoate) Category Challenge Submission

General

This submission included robust summaries for calcium bis(2-ethylhexanoate) and the SIDS Dossier for 2-ethylhexanoic acid. Summaries for potassium 2-ethylhexanoate submitted with the original Metal Carboxylates submission were used for this review.

Category Definition

The category consists of two substances, potassium 2-ethylhexanoate and calcium bis(2ethylhexanoate). The definition is clear and unambiguous.
Response: Noted

Category Justification

The combining of the two substances is adequately supported in that toxic effects are likely due primarily to 2-ethylhexanoate. The counter ions, an alkali metal and alkaline earth metal, respectively, are abundant in biological systems, well characterized, and are not expected to contribute directly to toxicity.
Response: Noted

Test Plan

On 22 May 2003, EPA commented that the original test plan did not adequately support the statement by the submitter that the bioavailability (and therefore the environmental fate, aquatic toxicity, and mammalian toxicity) of metal carboxylate salts would be equivalent to that of the separate metal ions and organic acids. The original test plan did not address the issue of the stability of metal-ligand complexes and only provided data for the acid/base (pKa, pKb) dissociation constants. The revised test plan still has not adequately addressed the use of the data on the dissociation products for the sponsored metal-ligand complexes. The submitter needs to provide a technical discussion on dissociation, with appropriate supporting experimental data on the dissociation of the metal-ligand complexes, and the bioequivalency of the dissociation products to the sponsored substances. As examples of more detailed discussions EPA refers the submitter to the technical discussions provided in the more recent submissions (especially the cobalt complexes) from the Metal Carboxylates Coalition (http://www.epa.gov/chemrtk/metalcarb/c14172tc.htm).
Response: see previous response

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

Adequate data were submitted for the melting point (potassium 2-ethylhexanoate), boiling point, vapor pressure and partition coefficient endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.
Response: Agree. Deficiencies in the physicochemical robust summaries for the calcium salt will be addressed.

Melting point. The submitter needs to provide measured melting point data for calcium 2-ethylhexanoate, according to OECD TG 102. EPA refers the submitter to Nora et. al (2002) at (www.mrw.interscience.wiley.com/ueic).
Response: The MP for calcium 2-EH is ca. 160 C. This information has been added to the robust summary.

Water solubility. Adequate data were submitted for potassium 2-ethylhexanoate. For the calcium salt, the submitted data range from 5 mg/L (estimated) to as high as 50 g/L (aquatic toxicity data). The submitter needs to provide measured water solubility data for the calcium salt according to OECD TG 105.

Response: See previous response.

Environmental Fate (photodegradation, stability in water, biodegradation and fugacity)

Adequate data were submitted for the photodegradation, biodegradation and fugacity endpoints for the purposes of the HPV Challenge Program.
Response: Noted.

Stability in water. A technical discussion needs to be included describing the multiple equilibria that occur during the dissociation of metal carboxylates. Although pH will have a strong effect on the stability of the metal-ligand complex, the tendency of the complex to dissociate is described by the metal-ligand dissociation constant (K) and not the acid-base dissociation constant (pKa and pKb). The submitter needs to distinguish these two dissociation equilibria in the discussion, especially as they pertain to water solubility.
Response: See previous response

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

All SIDS mammalian toxicity endpoints are satisfied by data on 2-ethylhexanoic acid. Although data for calcium octanoate (CAS No. 6107-56-8) were submitted for the acute toxicity and genetic toxicity (gene mutations) endpoints, there was no discussion in the test plan about the relevance of the analog.
Response: Data for calcium octoate (a synonym for Calcium bis(2-ethylhexanoate)) were submitted for the acute toxicity and genetic toxicity endpoints, not calcium octanoate. No change.

Ecological Effects (fish, invertebrates, and algae)

EPA reserves judgement for these endpoints. Critical data elements missing from key robust summaries for 2-ethylhexanoic acid need to be submitted before an independent evaluation can be rendered.
Response: Disagree. It is not the responsibility of the Metal Carboxylates Coalition to address deficiencies in the 2-ethyhexanoic acid robust study summaries since these were presented at SIAM 9 and updates of this document are the responsibility of the producers of that material.

Specific Comments on the Robust Summaries

General

The following comments apply particularly to the physicochemical and environmental fate robust summaries. In general, they did not provide enough detail. The submitter should consult EPA guidancedocuments for the preparation of robust summaries (http://www.epa.gov/opptintr/chemrtk/guidocs.htm).
Response: Noted.

Physicochemical Properties

The submitter needs to prepare robust summaries for the data cited in the test plan for all physicochemical endpoints.
Response: Agree. Robust summaries will be prepared for the data cited in the test plan for all physicochemical endpoints, where available.

Vapor pressure. Estimation methods are generally not reliable for inorganic salts, as the methods were derived for neutral organics. However, they are adequate in this case for the purposes of the HPV Challenge Program because they are near or below the guideline threshold value of $1x10^{-5}$ Pa. The submitter needs to state the limitations of the estimation method.
Response: The summary will be revised.

Environmental Fate

Photodegradation. The submitter needs to provide a technical discussion on the potential for direct photolysis for the category members.
Response: see previous response

Fugacity. The submitter needs to prepare robust summaries for the estimated data cited in the test plan including the modeling parameters used, since fugacity modeling has not been validated for salts.
Response: Agree. Robust summaries will be prepared for the estimated data.

Health Effects

Genetic toxicity (gene mutations). The summary needs to identify the positive controls for the calcium salt.
Response: Agree, this information will be provided for the following study:

- Van Goethem, D., 1980. Evaluation of calcium octoate in the Salmonella/Microsome (Ames) Assay. Study conducted for Tenneco Chemicals, Park 80 Plaza West – 1, Saddle Brook, NJ by Midwest Research Institute, Kansas City, MO (Study No. 4822-E)

The positive controls have already been provided for the following study:

- Van Goethem, D., 1981. Evaluation of calcium octoate, 5% in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Park 80 Plaza West – 1, Saddle Brook, NJ by Midwest Research Institute, Kansas City, MO (Study No. 4822-E)

Ecological Effects

The submitter needs to provide pH, dissolved oxygen, water temperature, number of replicates per test, and water hardness where applicable in the key robust summaries.
Response: Disagree. It is not the responsibility of the Metal Carboxylates Coalition to address deficiencies in the 2-ethyhexanoic acid robust study summaries since these were presented at SIAM 9 and updates of this document are the responsibility of the producers of that material.

Follow up Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.