201-15756

NCIC OPPT/DC/USEPA/US
Sent by: JuanB Perez

12/27/2004 08:39 AM

To NCIC HPV@EPA
cc
bcc
Subject Re: HPV Submisssion

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12/24/2004 03:41 PM

To NCIC OPPT@EPA, Rtk Chem@EPA
cc Ralph Parod <parodr@basf.com>
Subject HPV Submisssion

HPV Coordinator,

On behalf of BASF Corporation, I am submitting the test plan and robust summaries for the HPV substance "Distillation by-products from manufacture of 2-ethyl-1-hexanol" (CAS Number 68909-68-7). This is an update of a test plan and robust summaries originally submitted on 31 December 2003. The documents have been revised and are now ready for posting and review.

These documents are in PDF format (unlocked). If you have any questions or require the documents in another format please contact me by email or telephone

Best regards,

Elmer Rauckman, PhD, DABT (for BASF)

Toxicology and Regulatory Affairs

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618-539-5380


68609-68-7-TP.pdf


68609-68-7-RS.pdf

201-15756

Distillation by-products from manufacture of 2-ethyl-1-hexanol

CAS Number 68909-68-7

A Variable Mixture Also Know as:

- 2-Ethylhexanol distillation residuum
- 2-Ethylhexanol heavies
- EP-204
- Oxoel 800

U.S. EPA HPV Challenge Program Submission

December 31, 2003

Submitted by:

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Table of Contents

Executive Overview

The high-boiling fraction from the manufacture of 2-ethyl-1-hexanol CAS no. 68609-68-7 is known by several names in commerce including the more generic name "2-Ethylhexanol Heavies" as well as the more specific names "EP-204" (in the United States) and "Oxoel 800" (in Germany) that are used by BASF to designate this particular byproduct, which is called EP-204 in this document. EP-204 is a clear, pale yellow to green liquid with a mild characteristic odor. Most of the product is utilized for its heat value as a fuel and a portion is used in ore flotation applications. Annual production of EP-204 by BASF in the United States is estimated to be 3 to 5 million pounds and is limited to one plant. Production is in a closed system with storage in closed tanks. Shipping is limited to bulk transport by rail car or tank truck. Occupational exposure in manufacture is restricted by the use of essentially closed systems for production. Inhalation and dermal exposure during sampling and loading is controlled by the use of personal protective equipment. Inhalation exposure is also limited by low volatility. Available compositional information and the chemistry involved in the genesis of EP-204 are discussed in detail to understand the composition and possible components, and this information is used to conduct a hazard assessment of the material based on its known and possible components.

Some physicochemical, fate and toxicity studies have been conducted with commercial EP-204 and/or Oxoel 800. Studies have also been conducted on pure compounds and mixtures similar enough to EP-204 that they provide information relevant to defining the physicochemical properties and potential environmental and health effects of this mixture. EP-204 has a melting point of about -62°C and a boiling point range of about 180-350°C. Its vapor pressure at 20°C is 1-5 hPa and the components have log $K_{o/w}$ values ranging from about –0.48 to 5.17. Water solubility of the components ranges from less than 1 to greater than 1000 mg/L. Data on EP-204 itself indicates that it is 70% biodegradable in 28 days on an OECD 301B test; however, some components would probably be better characterized as inherently biodegradable. Examination of the major components indicate that the mixture is water stable, but components would be rapidly degraded in the atmosphere by indirect photolysis with a half-life from about 3 to 20 hours. If released into the environment in water it is expected to distribute primarily to water and sediment.

Hazard to aquatic organisms was estimated from the known aquatic toxicity of the major components. Based on the components it is estimated that this material will have low aquatic toxicity with EC_{50} values in the range of 3 to 100 mg/L. The limited solubility and high biodegradability also reduce environmental concern. Octanol-water partition coefficients were located or estimated for all identified components comprising 1% or more of the mixture. The log $K_{o/w}$ values (–0.48 to 5.17) combined with biodegradability and likely rapid metabolism indicate little propensity for bioaccumulation. Probable pathways of mammalian metabolism are discussed in detail; most pathways are similar to the metabolism of fatty nutrients to carbon dioxide.

EP-204 demonstrated an acute LD_{50} greater than 5000 mg/kg after oral gavage administration to rats of each sex. Oral toxicity data from components support an assessment of low acute toxicity. Saturated vapor exposure of rats

for 7 hours did not result in mortality or other significant clinical signs of toxicity. Acute dermal toxicity hazard is considered low based on data from representative components. No repeated administration studies are available for EP-204; however, several of its major components have been tested. Data from subchronic oral and inhalation testing of 2-ethylhexanol were selected as the most appropriate surrogate data to estimate the repeated-dose hazard of EP-204. Based on these data, EP-204 will probably cause peroxisome proliferation at high oral doses in the rat, but administration will be associated with few other effects at daily oral doses of 250 mg/kg or less. By inhalation exposure, no adverse effects are anticipated up to its saturation concentration in air. Repeated dose data from other components support an assessment of low repeated-exposure hazard.

Potential genetic effects were assessed via examination of adequate data for most of the major components of EP-204. The weight of evidence indicates lack of mutagenic or clastogenic activity for components of EP-204. No structural alerts were identified for any of the untested known components. Based on the chemistry, analysis of components by GC/MS and functional group analysis (by carbon-13 NMR), none of the unidentified components are anticipated to have genotoxic activity.

Lack of reproductive toxicity was indicated by the lack of effects on reproductive organs in repeated dose studies of components and surrogates and the lack of developmental toxicity for 2-ethylhexanol. In addition, no reproductive toxicity was observed in a one-generation dietary reproduction study of di-2-ethylhexyl adipate, which is another surrogate for EP-204 components.

Lack of developmental toxicity was also indicated by a National Toxicology Program gavage study with 2-ethylhexanol in mice where developmental toxicity was not observed at the highest dose tested (194 mg/kg-day). The dermal administration of 2-ethylhexanol to rats did not result in developmental toxicity even in the presence of maternal toxicity. A one-generation dietary reproduction study of di-2-ethylhexyl adipate in rats reported minor fetotoxicity at maternally toxic doses with a developmental NOAEL equivalent to ~ 120 mg/kg-day 2-ethylhexanol. In addition, the oral and dermal administration of another surrogate chemical, 2-ethyl-1,3-hexanediol, did not result in developmental toxicity below maternally toxic doses.

In summary, although this is a complex and variable mixture, enough is known about its chemistry and overall composition to derive a well-informed hazard characterization based on adequate studies of EP-204, components and surrogates. There is sufficient confidence in the hazard assessment to consider all the U.S. EPA HPV program data elements as being filled. No additional testing is recommended.

Testing Plan and Rationale

Testing Plan in Tabular Format

CAS No. 68609-68-7 EP-204	Information Available?	OECD Study ?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?	
HPV Endpoint								
Physical Chemical								
Melting Point	Y	N	N	Y	N	Y	N	
Boiling Point	Y	N	N	Y	N	Y	N	
Vapor Pressure	Y	N	N	Y	Y	Y	N	
Partition Coefficient	Y	N	N	N	Y	Y	N	
Water Solubility	Y	N	N	N	Y	Y	N	
Environmental & Fate								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	N	Y	N	Y	N	
Ecotoxicity								
Acute Fish	Y	N	N	Y	N	Y	N	
Acute Invertebrate	Y	N	N	Y	N	Y	N	
Acute Algae	Y	N	N	Y	N	Y	N	
Toxicity								
Acute	Y	N	?	Y	N	Y	N	
Repeated Dose	Y	N	Y	Y	N	Y	N	
Genetic Toxicology *"in vitro"*	Y	N	Y	Y	N	Y	N	
Genetic Toxicology "*in vivo*"	Y	N	N	Y	N	Y	N	
Reproductive	N	N	N	Y	N	Y	N	
Developmental	Y	Y	Y	Y	N	Y	N	

Introduction

The high-boiling fraction from the manufacture of 2-ethyl-1-hexanol CAS no. 68609-68-7 is known by several names in commerce including the more generic name "2-Ethylhexanol Heavies" and the more specific name "EP-204" used by BASF to designate this particular byproduct. The TSCA Inventory refers to this material as "1-Hexanol, 2-ethyl-, manuf. of, by-products from, distn. Residues" with the following description:

> The complex combination of hydrocarbons produced by the distillation of products from a 2-ethyl-1-hexanol manufacturing process. It consists predominantly of organic compounds such as alcohols, aldehydes, esters, carboxylic acids and acetals having carbon numbers predominantly in the range of C4 through C16 and boiling in the range of 199°C to 308°C (390°F to 586°F).
>
> Unknown, Variable, Complex, Biological Flag: UVCB

The TSCA Inventory description above is chemically broad, which is accurate in this case, as some of the actual components in this mixture have never been identified. Additionally, the TSCA definition allows for variations of the manufacturing process. In the case of the BASF material EP-204, the process used to produce 2-ethylhexanol is dimerization of n-butyraldehyde in the presence of base, hydrogen and a catalyst. The initial reaction is an aldol condensation that is followed by reductive dehydration and hydrogenation to produce 2-ethylhexanol. Although conditions are optimized to maximize the yield of 2-ethylhexanol, other reactions occur and the 2-ethylhexanol must be separated from by-products by fractional distillation. The material that is left behind from this distillation is the residue, often called "bottoms" or "heavies", from the distillation. Because this is a generic name for a product that could be produced using various ratios of feedstocks and even different chemical processes, the definition for CASNO 68609-68-7 is intentionally broad and somewhat vague. Although the BASF production is restricted to a single process, the byproducts remain variable because the primary objective of the chemistry is to produce maximal yields of high-purity 2-ethylhexanol. Consistency of byproduct composition is a secondary consideration.

Another variable is that the product is made both in the United States and in Germany. The German byproduct is called Oxoel 800 and it is nominally produced under the same conditions as US manufactured EP-204. The overall composition of Oxoel 800 is very similar to EP-204, and within the confines of the official TSCA definition for this CAS Registry Number, but the ratios of components may differ between US and German production at any given time. Other variables that apply to both the US and German production are that the distillation conditions can be temporarily modified to accommodate different purity grades of 2-ethylhexanol; and the activity of the catalyst decreases with time, which can alter distribution of products. The TSCA UVCB flag (Unknown, Variable, Complex, Biological Flag) applies well to this mixture, as it is an indeterminate mixture of chemicals some of which have not been definitively identified. As this document is written based on BASF production, conclusions may not be fully representative of CASNO 68609-68-7 in its broadest sense. For simplicity, the material called EP-204 in this document encompasses the Oxoel 800 produced in Germany but may not represent all variations of composition allowed under the TSCA definition of CASNO 68609-68-7.

EP-204 is a clear, pale yellow to green liquid with a mild characteristic odor (1). Industrial and commercial applications are listed as a "chemical solvent"; however, much of the product is utilized for its heat value as a fuel and a portion is used in ore flotation applications. Estimated annual production of EP-204 by BASF in the United States is in the range of 3 to 5 million pounds. United States production of the material is limited to one plant.

Production is in a closed continuous flow reaction system with product storage in closed tanks. Shipping is limited to bulk transport by rail car or tank truck. Occupational exposure in manufacture is restricted by the use of essentially closed systems for production. Inhalation and dermal exposure are possible during sampling and loading/unloading of rail cars/tank trucks but is controlled by the use of personal protective equipment when handling the material outside of the closed manufacturing system.

The composition of EP-204 is a critical aspect of this HPV analysis; thus, the chemistry of EP-204 formation and its typical composition are reviewed in detail in the "chemistry" section of this document.

Some physicochemical, fate and toxicity studies have been conducted with commercial EP-204 and/or Oxoel 800. Studies have also been conducted on pure compounds and mixtures similar enough to EP-204 that they provide information relevant to defining the physicochemical properties and potential environmental and health effects of EP-204. Studies on EP-204 and on appropriate surrogates are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. Where specific studies on EP-204 or Oxoel 800 have not been conducted, data from studies of major components or other surrogates are provided to fill the HPV endpoints. In some cases where calculated data are acceptable, a calculation based on the major components has been utilized for the SIDS parameter in question. The use of acceptable surrogates and adequate estimation methods are encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing cost and animal usage.

Chemistry

EP-204 (CASNO 68609-68-7) is an indeterminate mixture of variable composition derived as a byproduct from a chemical process. To appreciate how this material relates to other mixtures and pure chemicals that have relevant data and to comprehend the potential range of various components, it is valuable to understand the process and process variables that contribute to the production of this byproduct mixture.

EP-204 is a residue remaining from the aldol dimerization and dehydration of butyraldehyde under strongly basic conditions followed by hydrogenation in the presence of hydrogen and a catalyst. The intended reaction is addition of one butyraldehyde molecule to another to produce a transient alcohol that dehydrates to 2-ethylhexenal. The 2-ethylhexenal is reduced under these conditions to give 2-ethylhexanol – the desired product. Under the conditions employed, various side reactions occur to produce alternate materials, many of higher

molecular weight than 2-ethylhexanol. During the distillation phase of this continuous process, additional chemical reactions may occur to cause further condensation reactions of various components into higher molecular weight compounds through dehydration reactions. As the higher molecular weight compounds tend to be less volatile, they remain in the in the residue from the distillation. These distillation residues comprise EP-204.

The primary and intended reaction is an aldol condensation followed by reduction:

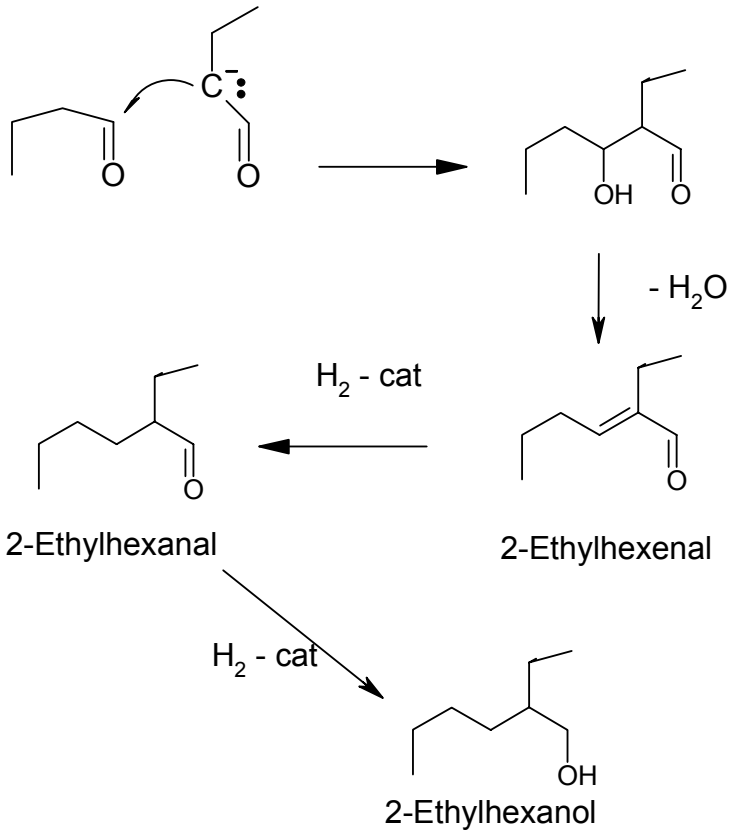

Figure 1. Intended Reaction to form 2-Ethylhexanol

In addition to this intended series of reactions, side reactions occur, such as addition of the butyraldehyde carbanion to 2-ethylhexanal to produce a 12-carbon compound. The number of potential byproducts is large, accounting for the complexity of EP-204 and the reason that some components remain unidentified. Chemistry of byproduct formation is discussed later in this testing plan. Table 1 gives the nominal range of chemicals, mostly as classes, comprising EP-204.

EP-204 Chemical Components	Weight % Approximate range
2-Ethylhexan-1-ol	2-15
Alcohols, C12 and higher	5-15
Diols, C8, C12 and higher	25-50
Alkyl ethers	2-20
Alkyl esters	5-15
Aliphatic hydrocarbons	5-7
Aliphatic aldehydes	0-2
Aliphatic acetals	0-5

Table 1. Categories of Components in EP-204

Additional characterization work has been conducted to categorize some of the individual components and the following components were identified by chromatographic techniques.

Chemical Component	CAS No.	Weight % Approx range
2,4-Diethyloctane-1,5-diol* (C12)	94277-83-5	5-40
2-Ethyl-1,3-hexanediol	94-96-2	5-15
2,4-Diethyloctane-1-ol		5-15
2-Ethylhexanol	104-76-7	5-15
2-Ethylhexenal	645-62-5	0-10
2-Ethylhexanal	123-05-7	0-10
n-Butyl-n-butyrate	109-21-7	1-5
2-Ethylhexyl-1,3-dibutyrate		0-4
n-Butanol	71-36-3	0-2
n-Butyraldehyde	123-72-8	0-2
2-Ethylhexyl-butyl ether	62625-25-6	0-5
* Tentative ID, could also be 2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol based on possible chemistry		

Table 2. Typical Composition of EP-204 (identified components)

In addition to this chromatographic characterization, a ^{13}C-NMR spectrum was recorded on current production material (specifically for this HPV submission) to gain assurance that the bulk product is composed of all aliphatic materials and to quantitate any aromatic carbons that might be present. The spectrum is shown as Figure 2; and it can be seen that there is a lack of aromatic carbons, further confirming the homogeneity of the material

regarding its aliphatic character. This indicates that cyclic- or polycylic-aromatic compounds are not present in the product.

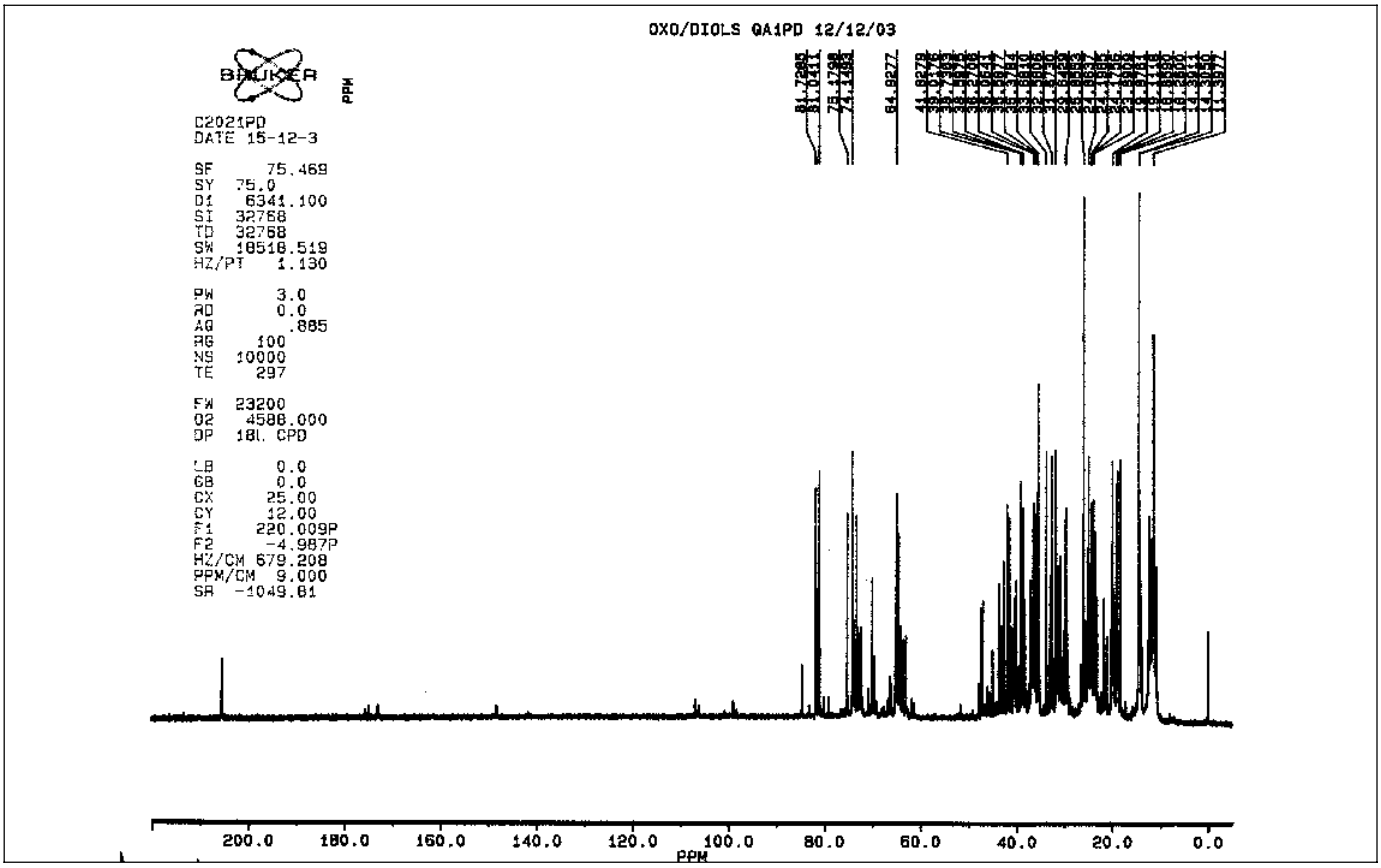

Figure 2. Carbon-13 NMR Spectrum of E-204

Tentative assignment of some of the carbon signals in this recent production run of EP-204 is useful in assessing the variety of structures contained in this mixture. It should be kept in mind that this is a sample of recent United States production at a particular time for this variable mixture and is not necessarily representative of all production.

The higher field lines (larger ppm chemical shifts) represent functional groups and quantitation (the nmr methodology is considered semi-quantitative) was derived from integration of the spectrum and has been normalized on the basis of 8-carbon units. The total percentage (on the basis of total carbon) of material containing functional groups (acetals, alcohols, esters and ethers) is a range of 70 to 110% with the remainder (0 to 30%) representing any saturated-hydrocarbon signals that are buried in the methylene and methyl carbon signals (Table 3).

Chemical Shift (ppm)	Tentative Identification	Approx Relative Percent
206	Aldehyde	< 5% of C8 groups
170-180	Esters	< 5% of C8 groups
99-108	Acetals, ethers	< 5% of C8 groups
80-82	Hindered alcohols or ethers	10-15 % of C8 groups
74-76	Ethers (1° or 2°) Alcohols (2°)	20-30 % of C8 groups
62-66	Alcohols (1°)	40-50 % of C8 groups
10-45	Saturated hydrocarbons [plus hydrocarbon chains of components, such as 2-EH]	Remainder

Table 3. Composition Based on NMR Data

Although this is only a semi-quantitative assessment of a "snapshot" sample we learn that the main category of component is primary alcohols with a significant contribution of secondary alcohols and/or ethers and very little material that could be characterized as an aldehyde or ester. This is consistent with the expected chemistry of the reaction system and, since one objective of the reaction is to convert an aldehyde to an alcohol (also a facile chemical reaction), we expect little free aldehyde or ester (also reducible) in the byproduct. Because the alcohols and ethers that are formed are stable to the reaction conditions, these molecules become "trapped" in the reaction mixture and do not undergo further reaction under these conditions. A consideration of the expected chemical reactions in this system provides further insight into the genesis and nature of EP-204 components.

Figure 3 shows the intended reaction and the probable genesis of some of the possible C-8 and C-12 diols. 2,4-Diethyloctane-1,3-diol, 3-ethyl-3-propyl-4-hydroxymethylhexane-1-ol and similar higher molecular mass compounds could be formed as shown by 1,2- or 1,4-addition of the butyraldehyde carbanion to 2-ethylhexenal. The reverse addition, where a carbanion derived from 2-ethylhexenal adds to butyraldehyde would be expected to generate yet another isomeric 12-carbon diol (2,4-diethyl-1,5-octanediol) as shown in Figure 4.

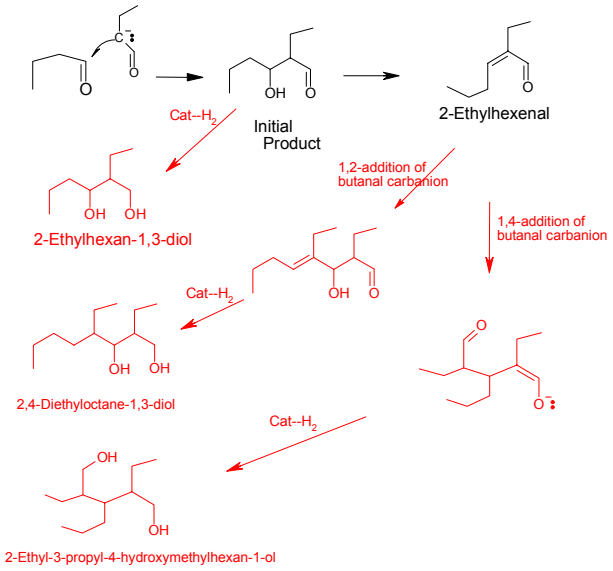

Figure 3. Formation of some C-8 and C-12 diols in EP-204

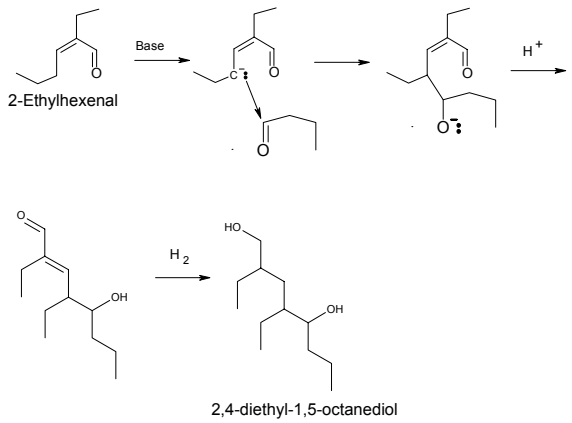

Figure 4. Possible Mechanism of 2,4-Diethyl-1,5-octanediol Formation

Analysis of some German production runs of material have indicated that as much as 40% of the mixture can be 2,4-diethyloctane-1,5-diol. This identification, however, is not unequivocal as isomeric materials with the same molecular mass and similar physicochemical properties, 2,4-diethyloctane-1,3-diol or 3-ethyl-3-propyl-4-hydroxymethylhexane-1-ol, could also account for this GC peak, or the peak could be a mixture of these isomers.

Figure 5 depicts the probable genesis of higher molecular weight diols in EP-204. The β-hydroxyaldehyde initial product from the aldol condensation loses water rapidly to produce 2-ethylhexenal. Although 2-Ethylhexenal is an intended intermediate in the production of 2-ethylhexanol, if it undergoes an addition reaction before it can be reduced it gives a 12-carbon intermediate that can in turn either be reduced or added to again with another 4-carbon unit to give the 16-carbon intermediate. This intermediate can likewise be reduced or add yet another 4-

carbon unit and so on. Moreover, it is possible to combine an 8-carbon carbanion derived from 2-ethylhexenal or 2-ethylhexanal (as in Figure 4) with a 12 or 16-carbon dialdehyde. The number of potential structures is large.

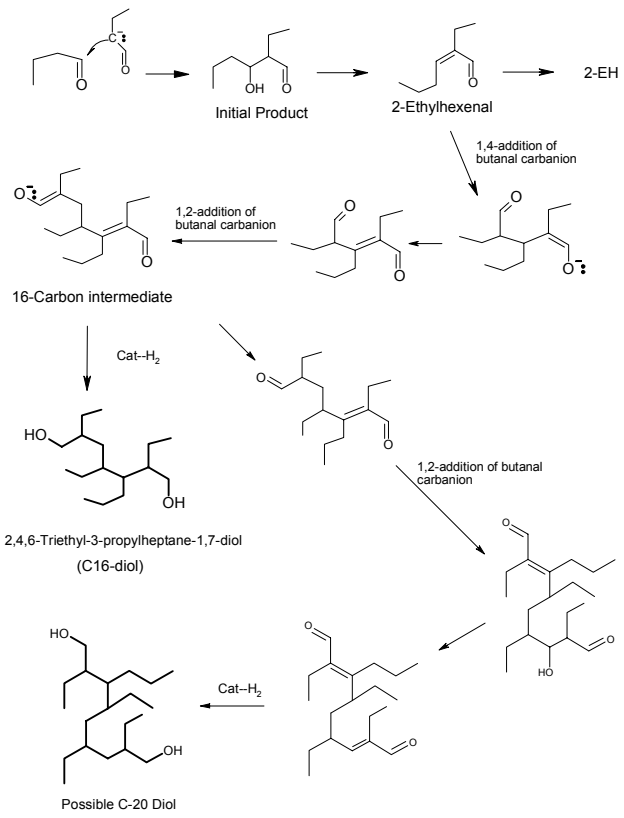

Figure 5. Potential Higher Diols Formation.

GC-Mass spectral analysis of a typical EP-204 sample, however, indicates (BASF internal data) that structures with carbon backbones greater than 12 carbons are not found at levels greater than one about percent of the mixture, as shown in Figure 6. Mass spectral analysis based on the molecular ion is a good indicator of the molecular weight of the components but cannot discriminate structural isomers without authentic chemical samples to use as standards; therefore, the structures labeled as "isomer" in Figure 6 represent only one possible structural isomer of the component with that empirical formula.

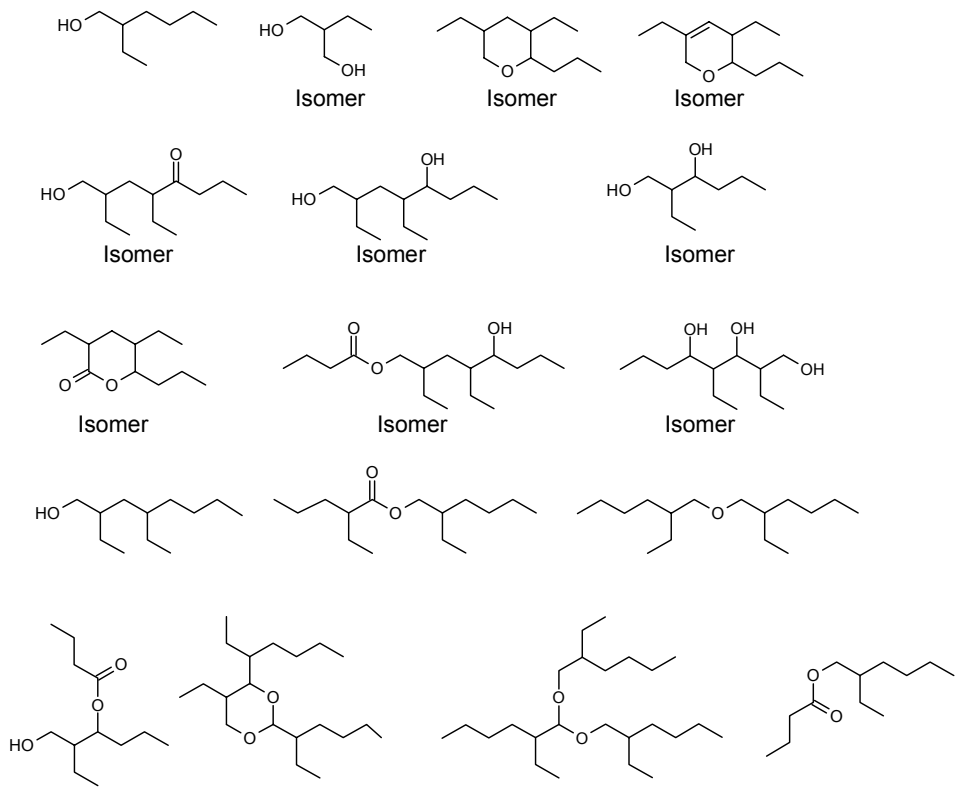

Figure 6. GC-MS Identification of All Components Above 1% in EP-204.
The structures marked "isomer" indicate that this is just one of several structural formulas for a material with this empirical formula

2,4-Diethyloctane-1-ol is another component that can be formed after dehydration of the initial product to 2-ethylhexenal followed by an aldol condensation. In some samples of German production material this byproduct has been identified at levels up to 10%. In Figure 7, two reaction paths that lead to its formation are depicted. This can be formed either by carbanion addition to 2-ethylhexenal (the initial dehydration product) or by carbanion addition to 2-ethylhexanal, which is formed by partial reduction of the α,β-unsaturated aldehyde. The exact mechanism of formation is irrelevant and is probably dependent on the activity of the hydrogenation catalyst. Of additional interest in this pathway is the intermediates A and B, which are both capable of 1,2 or 1,4 carbanion addition reactions leading to yet more byproduct structures.

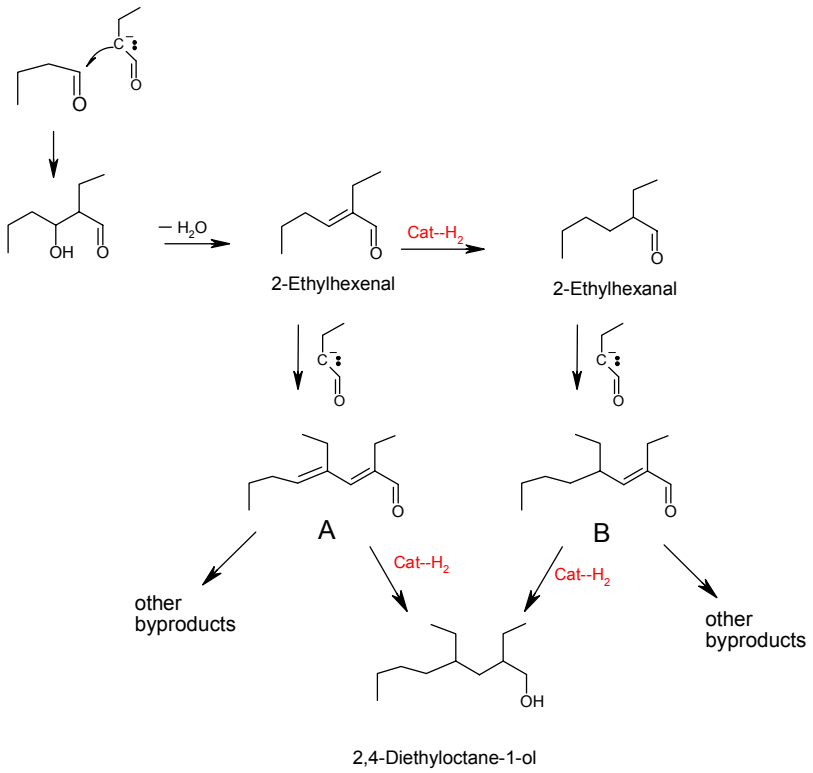

Figure 7. Mechanisms of 2,4-Diethyloctane-1-ol Formation.

What can be concluded by examination of the carbanion addition reactions (aldol condensations) is that this non-specific chemistry can produce numerous configurations of the carbon skeleton including diastereomeric isomers when the carbon skeleton reaches 12 carbons or greater and two or more asymmetric centers are present.

Figure 8 gives the presumed mechanism for ether formation and specific examples of probable ether structures that are expected under these reaction conditions. These structures are probably formed but may distill off the residue during the removal of 2-ethylhexanol leaving only higher molecular weight ethers such as di-2-ethylhexanol ether which was detected by GC-MS

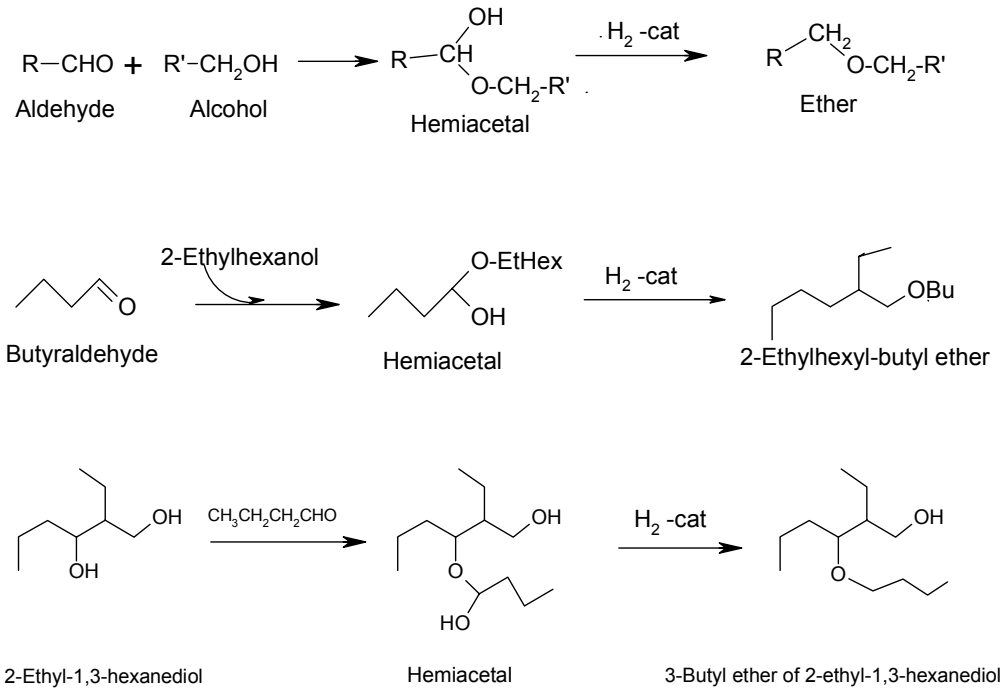

Figure 8. Ether Formation in EP-204

The last chemistry figure (Figure 9) gives the presumed mechanism for acetal formation and a specific example of a probable acetal formed in the reactions that could become a component of EP-204 but was not identified in the mass spectral analysis.

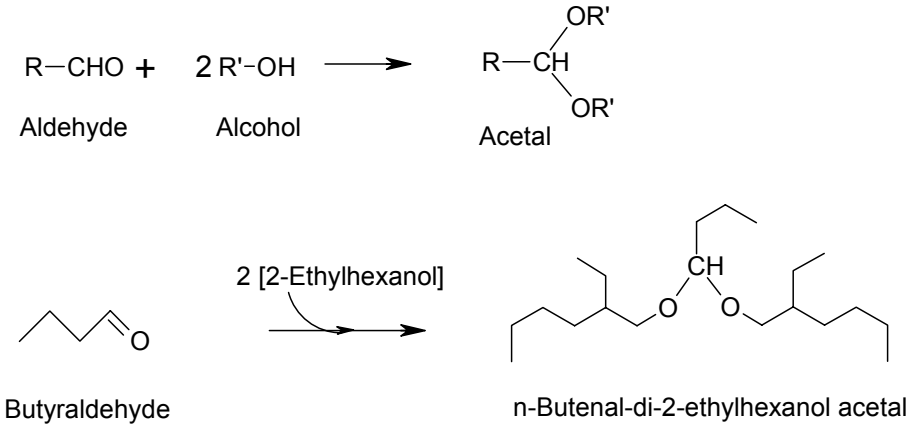

Figure 9. Acetal formation in EP-204

In summary, through carbon-13 and GC-MS characterization of current production material and through detailed consideration of the intended reactions and likely side reactions we have established that there is considerable structural diversity expected in both the size and configuration of the carbon skeleton. In addition, functional

groups produced in the reaction can be alcohols, ethers, acetals and esters. We have also established from the carbon-13 spectrum that alcohols (mono and diols) are currently the most prevalent functional group and based on the intended reaction (alcohol production) it is expected that alcohols will remain the prevalent species in EP-204 as reaction conditions undergo continual optimization to improve yield of 2-ethylhexanol. Thus, for the HPV hazard assessment of this material, it is logical to concentrate on the alcohols as the prime determinant of hazard unless there is reason to believe that one of the quantitatively lower level functional group categories is highly toxic, and as there is no rationale for that, the focus of hazard assessment for EP-204 will be on the alcohols which make up the bulk of the product.

Physicochemical Data

Physicochemical data for EP-204 are available from manufacturer's information and from EPIWIN estimates and are summarized in Table 4.

Melting Point	ca. –62˚ C (1, 2)
Boiling Point	ca. 180-350° C @ 1013 hPa (1, 2, 3)
Vapor Pressure	1 – 5 hPa @ 20˚ C (4)
Partition Coefficient	Variable Log $K_{o/w}$ = -0.48 to 5.17 (5)
Water Solubility	Variable, <1 to >1000 mg/L (5)

Table 4: Physicochemical Summary Data for EP-204

The melting point and boiling point range are measured properties for EP-204 (1, 2) and for Oxoel 800 (3) (which is the material produced by the same process in Germany by BASF). The boiling point is given as a wide range, typical of a material that undergoes fractional distillation as it boils. Likewise the freezing point is a measured property for typical production material but is expected to vary due to the variable composition.

A single octanol-water partition coefficient cannot be defined as this mixture has a variety of components that have individual hydrophobicities. To understand the potential distribution and bioaccumulative properties of EP-204, individual components must be taken into consideration. Table 5 contains the EPIWIN estimated log $K_{o/w}$ for the most prevalent components with concentrations estimated to be greater than 1% of the mixture. In addition to being the materials that actually make up most of EP-204, they represent a good cross section of the chemical classes that make up EP-204 and are considered representative of the entire sample (6). The $K_{o/w}$ spans from –0.48 for butyraldehyde to 5.17 for 2-ethylhexyl-1,3-dibutyrate. Although six of the materials have $K_{o/w}$ values equal to

or greater than 3 (indicating that bioaccumulation is possible), the one with the highest $K_{o/w}$ is an ester that is expected to be both biodegradable and easily metabolically converted by man and animals to a diol with a $K_{o/w}$ of 1.6 (see table). Most of the other components with high hydrophobicity are alcohols that are expected to be rapidly biodegraded in the environment and, if absorbed, can be metabolically conjugated to increase excretion. The only exception from the list below is the ether, 2-ethylhexyl-n-butyl. It is, however, a minor component (1% range) and expected to be inherently biodegradable and metabolically susceptible to oxidative transformation at a rate inconsistent with bioaccumulation.

Component	SMILES	log Kow*	H_2O Sol* (mg/L)
2-Ethylhexanol	CCCCC(CC)CO	2.73 c	880 e
2-Ethylhexenal	CCCC=C(CC)C=O	2.62 c	548.6 e
2-Ethylhexanal	CCCCC(CC)C=O	2.71 c	400 e
n-Butanol	CCCCO	0.88 e	63,200 e
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	1.60 c	4,200 e
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	5.17 c	0.567 e
n-Butyl-n-butyrate	CCCC(=O)OCCCC	2.83 c	309 c
n-Butyraldehyde	CCCC=O	-0.480 e	2385 e
2,4-Diethyloctane-1-ol	CCCCC(CC)CC(CC)CO	4.62 c	18.7 c
2,4-Diethyloctane-1,5-diol	CCCC(O)C(CC)CC(CC)CO	3.49 c	44.4 c
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol)	CCC(CO)C(CCC)C(CO)CC	3.49 c	44.4 c
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CCC(CO)CC(CC)C(CCC)C(CO)CC	4.89 c	1.69 c
2-Ethylhexyl-butyl ether	CCCCC(CC)COCCCC	4.90 c	3.32 c
* e = experimental value from SRC database, c = calculated value using EPIWIN			

Table 5: Water Solubility and Octanol-Water Partition Coefficients for EP-204

The vapor pressure of EP-204 is another variable parameter. Its initial vapor pressure will depend on the vapor pressure of the most volatile component and its physicochemical interactions with other components in the mixture. As the proportion of chemical components is variable, the initial vapor pressure will also be variable. In addition, as the mixture evaporates and loses the more volatile components, the nominal vapor pressure will decrease. The vapor pressure of typical bulk material was estimated from the initial boiling point using chemical principles (see robust summary). In the environment after dispersal, each component's individual vapor pressure will be a determinant in distribution of the chemical. Because of this, measured or estimated individual vapor pressures were used in the fugacity calculations describing hypothetical distribution. These individual component vapor pressures are available in the fugacity calculations given in the robust summary for distribution (see robust summaries).

Water solubility is dependent on both the water solubility of individual components and on the bulk properties of the material as a whole in equilibrium with water. When an organic liquid phase is present in water, the partition coefficient of an individual component is as important as its water solubility. In addition, with any partially water-soluble mixture, cosolvent effects are expected to play an important role. As EP-204 is a variable composition mixture and cosolvent effects are difficult to model, the experimental or calculated water solubilities are given as reference values, but it must be kept in mind that under varying conditions the effective solubility could be higher or lower. In consideration of the EP-204 composition being mostly higher molecular weight low solubility components, the mixture overall is expected to display relatively low water solubility and will form two phases when mixed with water.

Recommendation: No additional physicochemical studies are recommended. The available data fill the HPV required data elements with sufficient precision to define the hazards of this variable composition material.

Environmental Fate and Pathways

Biodegradation potential has been determined using carbon dioxide evolution (OECD guideline 301B). EP-204 (tested as Oxooel 800) was found to be 70% biodegradable (as percent of theoretical carbon dioxide evolution) in 28 days (7). Although this indicates the material is biodegradable, the time required to achieve 60% biodegradation was not short enough to meet the definition of "readily biodegradable" by the OECD criteria. This information is consistent with the structures of the most prevalent compounds, many of which are considered readily biodegradable; however, some of the individual components with linear and branched ether structures are probably better characterized as "inherently biodegradable". Based on inspection of the chemical structures, no component is anticipated to be resistant to biodegradation.

Most of the components are considered stable to hydrolysis, as they do not contain a hydrolysable group. The major exception to this is the esters and although they are theoretically hydrolysable, they are predicted by the HYDROWIN Program (v1.67) to have half-lives grater than one year in water at pH 7 (Table 6).

Component	Total K_b (L/mol-sec)	Hydrolysis Half-live	
		pH 8.0	pH 7.0
2-Ethylhexyl-1,3-dibutyrate	3.561×10^{-2}	225 days	6.2 years
n-Butyl-n-butyrate	5.317×10^{-2}	151 days	4.1 years

Table 6. Predicted Hydrolytic Stability of Ester Components of EP-204

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The approach used was to take the most prevalent identified materials in the preparation and individually determine their reactivity with hydroxyl radical assuming each component will be unaffected by the others after vaporization into the troposphere. The program produced estimated rate constants ranging from 6.89×10^{-12} to 50.0×10^{-12} cm^3/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the range of estimated rate constants of major components of EP-204 for reaction with hydroxyl radical, the estimated half-life of EP-204 vapor in air is approximately 3 to 20 hours. The full details of the calculations are given in the robust summaries and Table 7 provides a summary of the results from these calculations. Photodegradation of the lower level and unidentified components is expected to be facile; as these components have similar empirical formulas and functional groups, their rate constants for reaction with hydroxyl radical will be similar.

Component	SMILES	Results of AOP v 1.09 Hydroxyl Radical Reaction Prediction	
		Rate Constant ($x10^{12}$ cm/molec-sec)	Half-life (hrs)
2-Ethylhexanol	CCCCC(CC)CO	13.2	9.7
2-Ethylhexenal	CCCC=C(CC)C=O	50.0	2.6
2-Ethylhexanal	CCCCC(CC)C=O	34.0	3.8
n-Butanol	CCCCO	6.89	19
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	22.2	5.8
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	17.5	7.3
n-Butyl-n-butyrate	CCCC(=O)OCCCC	10.6	12
n-Butyraldehyde	CCCC=O	25.4	5.0
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol)	CCC(CO)C(CCC)C(CO)CC	24.5	5.2
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CC(CO)CC(CC)C(CCC)C(CO)CC	29.3	4.4
2-Ethylhexyl-n-butyl ether	CCCCC(CC)COCCCC	35.1	3.7

Table 7. Summary of Photodegradation Estimates

As shown by the calculations (see robust summaries), the primary reaction for this series of components is hydrogen abstraction, the rate of which increases linearly as the number of hydrogen atoms in the molecule increase. The ether moiety activates adjacent hydrogen atoms toward radical abstraction while the ester has a deactivating influence giving the esters a longer predicted half-life. Based on the chemical structures of EP-204 components, reaction with ozone will not be important. In addition, none of the materials will absorb light above 290 nm; thus, direct photolysis in the troposphere will not be significant. In summary, all components are expected to have relatively short atmospheric half-lives reacting primarily with atmospheric hydroxyl radical.

Theoretical Distribution (Fugacity) of EP-204 in the environment was estimated using the MacKay EQC level III model in EPIWIN v 3.05 using release only to water, (considered the most likely situation) as the means of entry into the environment. The approach used was to take the ten materials known or expected to be in the in the mixture in the greatest quantity and individually determine their fugacity assuming that one component will not significantly affect the distribution of the other after dispersal. As the measured vapor pressure of EP-204 is a function of the partial pressures of each component, it is more appropriate to use the EPIWIN predicted vapor

pressure for each component in the calculation. Likewise, individual predicted values for log K_{ow}, K_{oc}, and half-lives were utilized. The biodegradation half-lives that were utilized were EPIWIN generated but were evaluated for consistency with the known biodegradability of the preparation and found to be representative.

The entire data set with the values utilized for all parameters is shown in the Robust Summary for distribution in the environment and a summary is shown in Table 8. The components evaluated are representative of the full spectrum of components contained in EP-204 and include alcohols, diols, aldehydes, an α,β-unsaturated aldehyde and esters. Examination of Table 8 reveals that the EP-204 components distribute primarily to water. The more volatile components have some distribution to air and 2-ethylhexyl-1,3-dibutyrate; 2,4-diethyloctane-1-ol and 2,4,6-triethyl-3-propylheptane-1,7-diol (the C16-diol) have significant predicted distributions in sediment. Soil distribution is not considered to be important for any component under these conditions of 100% release to water. Not apparent from this summary table, because the distribution is normalized to 100%, are the magnitude of initial loss of material to biodegradation in a waste-treatment plant and the relatively short half-lives of the components in the environment due to biodegradation and indirect photolysis.

Component	SMILES	Distribution (Percent)			
		Air	Water	Soil	Sediment
2-Ethylhexanol	CCCCC(CC)CO	0.52	98.9	0.02	0.52
2-Ethylhexenal	CCCC=C(CC)C=O	0.94	98.4	0.01	0.61
2-Ethylhexanal	CCCCC(CC)C=O	1.81	97.5	0.01	0.67
n-Butanol	CCCCO	2.55	99.6	0.02	0.16
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	<0.1	99.8	0.01	0.22
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	0.03	55.5	0.01	44.4
n-Butyl-n-butyrate	CCCC(=O)OCCCC	4.51	94.9	0.03	0.56
n-Butyraldehyde	CCCC=O	1.07	98.7	0.01	0.18
2,4-Diethyloctane-1-ol	CCCCC(CC)CC(CC)CO	0.87	79.6	0.02	19.6
2,4-Diethyloctane-1,5-diol	CCCC(O)C(CC)CC(CC)CO	0.02	97.6	0.02	2.35
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol-2)	CCC(CO)C(CCC)C(CO)CC	0.03	97.6	0.02	2.35
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CC(CO)CC(CC)C(CCC)C(CO)CC	0.04	69.3	0.06	30.6
2-Ethylhexyl-n-butyl ether	CCCCC(CC)COCCCC	1.74	77.4	0.01	20.9

Table 8: Theoretical Distribution (Fugacity) of EP-204 **in the environment**

Recommendation: No additional fate and pathway studies are recommended. The available data fill the HPV required data elements.

Ecotoxicity

A guideline-compliant daphnia study has been conducted on an analyzed sample of EP-204 (test material was Oxoel 800) giving a 48-hour EC_{50} of 52 mg/L (8). Studies on fish and algae have not been conducted with the subject mixture; however, experimental data for invertebrates and algae are available for many of the major components of EP-204. Aquatic toxicity of other components can be estimated using ECOSAR and the appropriate QSAR model. It is believed that the aquatic toxicity of EP-204 can be adequately defined by the toxicity of its individual components and by the single daphnia test. The good correlation between the component-predicted toxicity and the empirical daphnia data (*vide post*) supports this methodology as a conservative means of assessing the aquatic toxicity of this substance.

Experimental and modeling data for aquatic toxicity of the major components of EP-204 are shown in Table 9. In addition to experimental data for all three throphic level endpoints on 2-Ethylhexanol; 2-Ethexenal; 2-Ethylhexeneal and n-Butanol, studies on fish (fingerling channel catfish) have been reported for 2-Ethylhexyl-1,3-diol in the EPA ECOTOX database indicating an LC_{50} of 624 mg/L for a 96-hour exposure. Studies on daphnia or green algae, however, were not located in the open literature for this component.

Aquatic Toxicity (mg/L)						
	2-EH	2-Ethexenal	2-Ethexanal	n-Butanol	2-Ethylhexyl-1,3-diol	C-12 diol
Fish, 96-hr LC_{50}	17-30 (9)[§]	6.0 (10)	8 (11)	> 1000 (12)	257* [624][†]	6.0*
Daphnia, 48-hr EC_{50}	39 (9)	20 (13)	11.5 (14)	> 1000 (12)	268*	7.1*
Algae, 96-hr EC_{50}	10-20 (9)	19.3 (15)	52 (14)	> 100 (12)	164*	4.8*

§ Numbers in parentheses are references.

* Estimated using ECOSAR (16)

[†] Experimental LC_{50} of 624 mg/L reported in EPA ECOTOX database (17)

Table 9: Aquatic Toxicity of EP-204 Components.

Determination or estimation of the actual ecotoxicity values and the actual solubility of EP-204 under environmental conditions is complicated by the fact that it is a variable composition mixture and, in addition, potential environmental conditions are variable. The aldehydes, which are expected to be more toxic to aquatic species than the neutral organics (based on the ECOSAR specific aldehydes model), tend to be minor components of this mixture. Examination of the composition Tables 1, 2 and 3 (*vide ante*) indicates that the major components are alcohols and diols, with a high proportion of C-8 and C-12 carbon chains. Modeling and experimental data included in Table 9 indicate that the diols are less toxic to aquatic life than the mono-alcohols and that the C-8 diol is of low toxicity and the C-12 is probably moderately toxic.

If the components are lumped together, assuming no specific joint-toxic action and the same mechanism of action, a rough estimate of the toxicity of EP-204 can be calculated using the principle of additivity. This is done by

summing the component's fraction divided by the LC_{50} or EC_{50}, dividing this by the sum of the fractions and taking the reciprocal. The L/EC_{50} values used are the experimental or estimated single values or the geometric mean if a range of L/EC_{50} values is given in Table 9. The calculation for the estimated LC_{50} for fish is given below as an example. All calculations are given in the attached robust summaries.

Example Calculation of Estimated LC_{50} for Fish				
Component	[%]	LC_{50} (mg/L)	$1/LC_{50}$	x[%]
2,4-Diethyloctane-1,5-diol* (C12)	22.5	6.0	0.166667	3.75
2-Ethyl-1,3-hexanediol	10	257	0.003891	0.038911
2-Ethylhexanol	10	24.4	0.040984	0.409836
2-Ethylhexenal	5	6	0.166667	0.833333
2-Ethylhexanal	5	8	0.125	0.625
n-Butanol	1	1000	0.001	0.001
%Total	[53.5]		Σ	5.65808
		Div Tot [%]		0.105759
		1/x = Estimated LC_{50}		9.5

The Estimated LC_{50} or EC_{50} for fish, daphnids and algae are:

- Fish 9.5 mg/L
- Daphnids 13 mg/L
- Green Algae 9.3 mg/L

Realistically, given the variability of the bioassays used to determine the toxicity of the individual components and the variability of the mixture, a range for these LC_{50} and EC_{50} values of 3 to 100 mg/L is considered probable for EP-204. As a test of these calculations, there are experimental Daphnia magna data showing a 48-hour EC_{50} of 52 mg/L (8). This is certainly in the range suggested above but about 5 fold higher than the calculated value; however, it was remarked in the laboratory report that the test substance was "not completely soluble in the tested concentration range".

Analysis of the EP-204 lot (test material was Oxoel 800) used to expose Daphnia is shown in Table 10. In addition, the table contains columns giving the experimental (e) or predicted (p) water solubility and the experimental (e) or predicted (p) daphnia 48-hour EC_{50} for each component. The final column is the calculated concentration of each individual component at a concentration of 50 mg/L (the EC_{50}) of the whole material.

Examination of Table 10 reveals that at the EC_{50} of 52 mg/L, all the identified major components are predicted to be fully soluble; however, some may have partitioned into the small amount of insoluble material observed in the test vessel. The insoluble material may be high molecular weight components from the "high-boiling components". It can be concluded that a typical sample of EP-204 is of low toxicity to daphnia in spite of the

ECOSAR prediction of a lower LC_{50} due to the presence of diethyloctanol in this particular sample at 5 to 10%. It is further concluded that these components do not have an apparent synergistic activity on one another and estimation of aquatic toxicity for this mixture by estimation from the components is a conservative way to evaluate the aquatic hazard of EP-204.

Component (test material was Oxoel 800)	Percent	Water Solubility (mg/L)	[Component] (mg/L) at 50 mg/L EP-204	EC_{50} (mg/L)
2,4-Diethyl-1,5-octanediol	51.9	44.4 (p)	26 (p)	7.1 (p)
2-Ethyl-1,3-hexanediol	9.1	4200 (e)	4.5 (p)	268 (p)
2-Ethylhexanol	12.6	880 (e)	6.3 (p)	39 (e)
Diethyloctanol	5-10	18.7 (p)	2.5-5 (p)	0.6 (p)
High-boiling components	20	Unknown Possibly < 1	10 (p)	?

Table 10. Analysis of EP-204 sample used for daphnia study.

In addition to solubility, persistence of these alcoholic components is another issue that should be considered in the aquatic-hazard assessment of EP-204. Aquatic toxicity and solubility have an inverse relationship for the neutral organic components of EP-204; thus, the more toxic materials are expected to be of lower solubility reducing their aquatic toxicity hazard. It has been determined that EP-204 is readily biodegradable and while this determination was for only one production run, this finding and structural examination of the most prevalent components suggest that none will be resistant to bacterial action in the environment.

Recommendation: No additional ecotoxicity studies are recommended. The available information fills the HPV required data elements.

Health Effects

An acute oral toxicity study has been conducted on commercial EP-204 (test substance Oxoel 800) showing an LD_{50} in male and female rates greater than 5000 mg/kg without indications of specific toxic effects (18). Several studies have been conducted on individual components of EP-204 that cover repeat dose, reproductive and developmental endpoints. Especially relevant are toxicity studies of 2-ethylhexanol and 2-ethyl-1,3-hexanediol.

2-Ethylhexanol is a high volume chemical used in the manufacture of plasticizers such as diethylhexyl phthalate and diethylhexyl adipate. As a result of the plasticizer end use and potential for consumer exposure, 2-ethylhexanol has been well studied toxicologically.

In the past, 2-ethyl-1,3-hexanediol was used commercially as an insect repellent and is still used today as a solvent in cosmetics. The pesticide registration was voluntarily withdrawn after a developmental toxicity study showed malformations in rat fetuses at maternally toxic doses. Because of this former use as an insect repellent and current use in cosmetics, this material has been fairly well studied regarding toxicity, especially by the dermal route. Since withdrawal of its pesticide registration and use as an insect repellent, fewer new studies have been reported.

2-Ethyl-1,3-hexanediol has been nominated to the NTP as a candidate for reproductive and developmental studies. Its current NTP status is "Deferred pending an evaluation of an industry study and EPA's risk management assessment". The safety of 2-ethyl-1,3-hexanediol as a solvent in cosmetics was reviewed for FDA by the Cosmetics Ingredients Review (CIR) Expert Panel and their published conclusion is "safe as used in concentrations up to five percent" (19).

Metabolism

Adsorption, distribution, metabolism and excretion are important processes that facilitate an understanding of the potential health effects of a material and allow the extrapolation of data among studies and routes of exposure. This is particularly true in the case of EP-204 where common metabolic routes, fates and inter-conversions of the individual EP-204 components justify the use of data from representative components to evaluate the health hazard of the commercial product.

It is postulated that most EP-204 components are metabolized by oxidation to a carboxylic acid and then either conjugated and excreted or are broken down fully by a series of oxidation reactions (primarily beta oxidation). Thus, after the initial oxidation of the alcohol by dehydrogenases, the fatty acid metabolism system treats the resulting carboxylic acids as fatty nutrients. The final products are carbon dioxide and acetyl-CoA with formation of ATP along the way. Several published studies support this hypothesis.

It is known that after oral administration, 80% of the absorbed 2-ethylhexanol is excreted in the urine and only about 6% is expired as carbon dioxide. In the rat, 2-ethylhexanol is initially rapidly oxidized to 2-ethylhexanoic acid and then apparently conjugated and filtered by the kidney faster than it can be metabolized via beta oxidation. Presumably, the carbon dioxide is formed primarily by beta oxidation of 2- ethylhexanoic acid. Evidence for beta oxidation also comes from the identification of small quantities of 2- and 4-heptanone in the urine, which are formed by a partial beta oxidation followed by decarboxylation rather than beta scission (20).

In a study of 2-ethyl-1,3-hexanediol metabolism, investigators were unable to detect any metabolites when 2-ethyl-1,3-hexanediol was fed to rabbits (21). This suggests that the metabolism of 2-ethyl-1,3-hexanediol via beta oxidation proceeds more readily than that of 2-ethylhexanol. Additional confirmation comes from a

pharmacokinetics study of (1,3-^{14}C)- 2-ethyl-1,3-hexanediol that was conducted following iv dosing of male Fischer 344 rats. Pharmacokinetic analyses of the plasma data indicated that there is dose linearity in the 1.5 to 150 mg/kg range, and that 2-ethyl-1,3-hexanediol is cleared from plasma in a bi-exponential manner according to first order transfer and elimination processes. The data show that 2-ethyl-1,3-hexanediol-derived radioactivity is rapidly distributed and then slowly eliminated probably as metabolites over a 48 hr period after a single iv injection. 2-Ethyl-1,3-hexanediol is not found in the urine as unchanged test material, which also indicates that this chemical is probably completely metabolized in the rat (22).

If the structures of 2-ethylhexanol and 2-ethyl-1,3-hexanediol are examined with regard to the biochemical events that are responsible for beta oxidation, this difference in elimination – primarily urinary excretion (2-ethylhexanol) versus complete metabolism (2-ethyl-1,3-hexanediol) - is logical. Figure 10 gives the structures of the EP-204 components 2-ethylhexanol and 2-ethyl-1,3-hexanediol. As beta-oxidation requires several distinct steps and as 2-ethyl-1,3-hexanediol has the beta carbon in an oxidized state already, it is well down the beta-oxidation pathway as it is absorbed. On the other hand, 2-ethylhexanol requires several metabolic steps before undergoing beta oxidation. As these steps require time and cofactors, there is more opportunity for renal filtration to remove a significant portion as the unchanged 2-ethylhexanol or its conjugated initial metabolite.

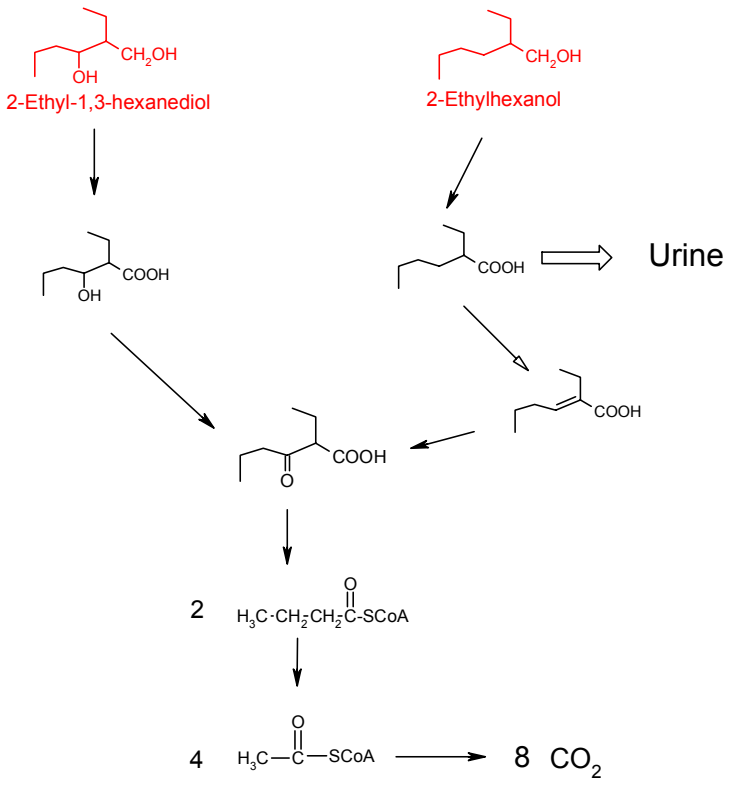

Figure 10. Major Excretion Routes for 2-Ethylhexanol and 2-Ethyl-1,3-hexanediol.

No information on the metabolism of higher congeners was located but based on the similarity in structure of these congeners with 2-ethyl-1,3-hexanediol, and their greater lipophilicity, it is anticipated that they compete favorably for beta oxidation rather than being excreted readily in the urine. It can be seen in Figure 11 that beta oxidation is an available option for the C-12 mono alcohol. Similarly, the C-12 diol (2,4-diethyl-1,5-octanediol) that was the major component of the EP-204 used in the daphnid test could be subject to beta oxidation; and it is pre-oxidized for the second round of beta oxidation. All of these metabolic schemes feed into the common intermediate 5-keto-2-ethylhexanoic acid that will undergo scission to two CoA conjugates of butyric acid, and on to acetyl CoA and finally carbon dioxide. The esters, acetals and ethers all will fit into this same metabolic scheme after hydrolysis or ether cleavage.

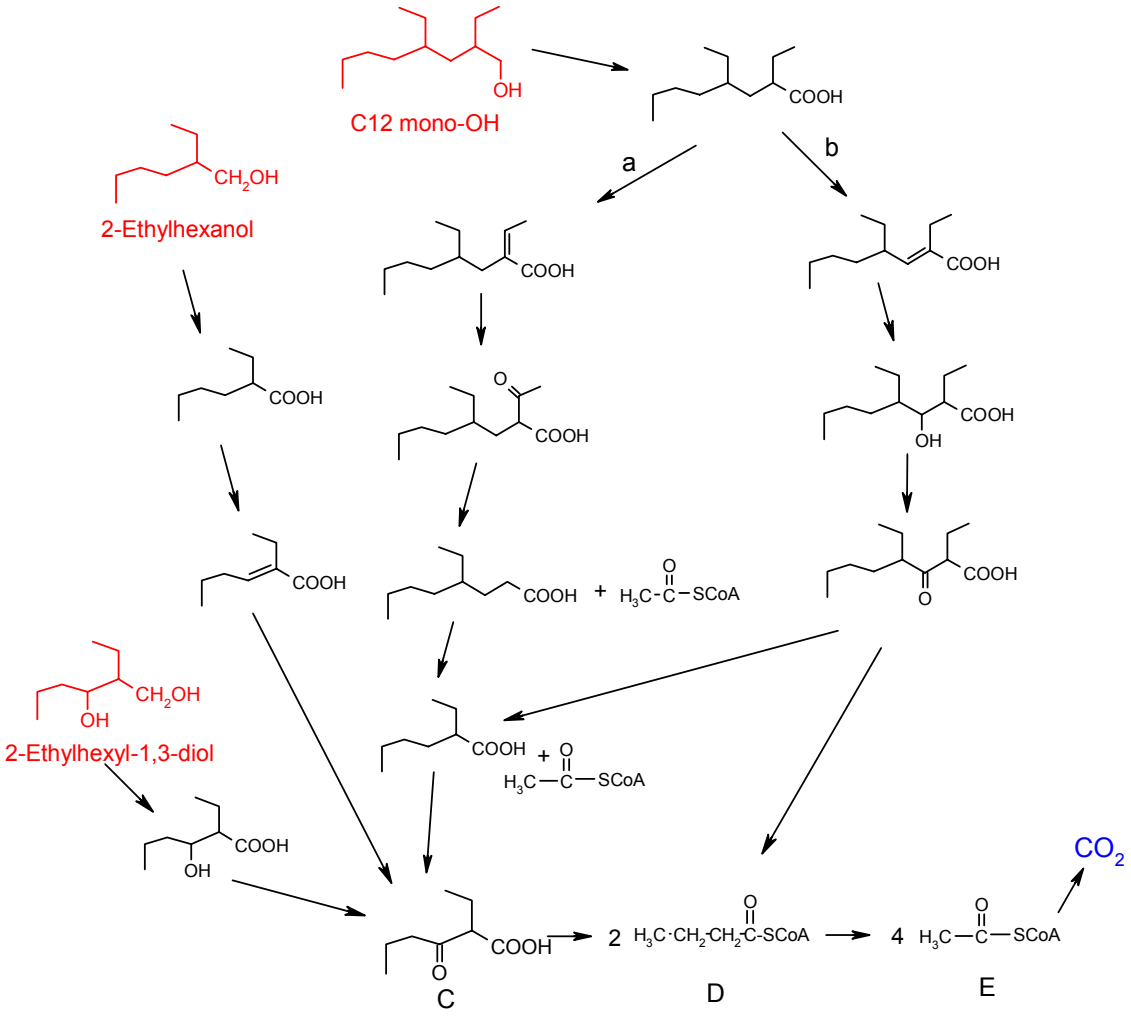

Figure 11. Common Metabolic Pathways of Major Components

In light of the similarity in structure of the most prevalent components of EP-204 and with the existence of a likely common metabolic path, the use of 2-ethylhexanol and 2-ethyl-1,3-hexanediol as surrogates for the entire mixture appears to be a logical and rational approach to understanding the hazard of EP-204.

Acute Toxicity

Oral Exposure

The oral LD_{50} of EP-204 (test substance was Oxoel) was determined in rats to be greater than 5,000 mg/kg. This study used groups of 5 Wistar rats of each sex and a "limit-test" design at a 5000-mg/kg dose level. Mortality was reported only in 2/5 females that died within 48-hours of dosing. Clinical signs were indicative of narcosis but were generally unremarkable. No chemically-related findings were reported at necropsy.

This low toxicity of the mixture is consistent with available data on the components. One of the components expected to be more toxic, 2-ethylhexanal, has been found to have an oral LD_{50} in rats between 2,626 and 3,730 mg/kg body weight (23). Likewise, the acute LD_{50} for 2-ethylhexenal is reported as 3,000 mg/kg in rats (24). The C-8 diol 2-ethyl-1,3-hexanediol has a reported oral LD_{50} of 1,300 mg/kg (25) and the acute-oral toxicity of 2-ethylhexanol in rats is low with an LD_{50} between 2049 and 7000 mg/kg (26).

The testing of a production sample of the actual chemical mixture and finding it less acutely toxic than some of its components provides some assurance that the components are not acting synergistically to produce excess acute toxicity. Although this observation does not preclude synergism in repeated-dose studies, it mitigates the concern regarding synergistic action.

Inhalation Exposure

Low volatility limits the vapor inhalation hazard for EP-204, which is essentially a distillation residue. Verification of this comes form an acute inhalation study conducted by BASF on Oxoel 800. In this study, six rats of each sex were exposed to a saturated vapor of the test material generated at 20° C for a period of 7 hours (27). The nominal concentration calculated from the flow rate and material loss was 0.11 mg/L. No animals died during exposure or in the 14-day observation period. No significant clinical signs were observed.

Available data on components support a low level of inhalation toxicity. A subchronic inhalation study using an essentially saturated concentration of 2-ethylhexanol vapors (120 ppm) has been conducted with no mortality after 13-weeks of exposure for 6 hours a day. The aldehyde components are potential inhalation hazards but they are such strong respiratory irritants that significant exposure of workers is considered unlikely (28).

Dermal Exposure

Although the acute dermal toxicity of EP-204 itself has not been reported, there is a report of a dermal test of "2-Ethylhexanol – Heavy Parts" tested under the same CAS No. The value given for the dermal LD_{50} of this material in the rat is > 1740 mg/kg (29). This value is consistent with the dermal LD_{50s} of potential 2-Ethylhexanol – Heavy Parts" components; however, neither compositional data of the tested material nor details of the study are available.

Available data from components confirm low dermal toxicity. The acute LD_{50} of 2-ethylhexanal in the rabbit has been reported to be 4235 mg/kg (23). The acute LD_{50} of 2-ethylhexenal in the guinea pig is greater than 20 ml/kg (30). 2-Ethylhexanol is reported to have a rabbit dermal LD_{50} between 1980 and >2600 mg/kg and a rat dermal LD50 >3000 mg/kg body weight (26). Pregnant rats all survived dermal application of 4 ml/kg of 2-ethylhexyl-1,3-diol for 10 consecutive days (31).

Recommendation: No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet all the requirements of the current OECD guidelines in all cases, the weight of evidence shows that the oral, dermal and inhalation toxicity hazard is very low. Conduct of additional studies would not add significantly to our understanding of this material's toxicity and it is recommended that no additional acute toxicity studies be conducted.

Repeated Dose Toxicity

Oral Exposure

No repeated dose studies have been conducted on EP-204 itself, but several of its components have been investigated in repeated-dose studies. Based on the variety of possible structures contained in EP-204, the components and surrogates below are considered to be reasonably predictive of the repeated dose hazard of EP-204. Supporting this contention are metabolic data from 2-ethylhexanol that show complete metabolism of this substance to carbon dioxide and products of intermediary metabolism is possible (although urinary excretion of conjugates is normally an important means of excretion). As the C-8 aldehydes metabolically interconvert with 2-ethylhexanol, and as the higher homologs have the same basic structural components, all components are anticipated to be fully degraded in mammals by means of shared metabolic pathways initiated by oxidation to a carboxylic acid followed by a series of beta oxidations to four and two carbon compounds that are excreted (e.g. carbon dioxide) or incorporated into intermediary metabolism. The point being that these compounds can be handled by the body in a manner similar to nutrients without the build up of non-metabolizable or reactive structures; thus, adverse effects are considered unlikely after low-level exposure.

Recently conducted 13-week (32) and 2-year (33) studies are available for 2-ethylhexanol by oral gavage. In the 13-week study, groups of rats (10 animals of each sex) received daily oral gavage doses of 0, 25, 125, 250 or 500 mg/kg on 5 consecutive days per week for 13 weeks. Peroxisome proliferation was also determined in satellite groups of animals. The 500-mg/kg dose was associated with significant peroxisome proliferation and systemic toxicity as evidenced by a small but statistically significant ($p < 0.01$) reduction in body weight gain in rats of each sex. Target organs were the liver (increased organ weights with peroxisome proliferation and decreased peripheral lobular fatty infiltrate) and forestomach (acanthosis in the mucosa). There was also a slight increase in relative testis weight at 500 mg/kg but this was not correlated with any morphological changes. Reduced relative ovarian weights were seen at 250 mg/kg but did not occur at 500 mg/kg and were considered incidental, as there was no morphological correlate. It was concluded that 125 mg/kg was the NOEL based on treatment-related organ weight changes at 250 mg/kg (increased relative liver and kidney weights in males and females). The primary "adverse" effect was peroxisome proliferation noted in the 500 mg/kg males and females. Based on the results, the NOAEL was considered to be 250 mg/kg as the liver and kidney weight changes were probably adaptive since no histopathologic correlates were reported.

Chronic toxicity and carcinogenicity studies of 2-ethylhexanol in Fischer-344 rats were conducted at 50, 150, or 500 mg/kg/day 2-ethylhexanol by oral gavage for 24 months. Females showed a dose related increase in mortality, with 52% mortality at 500 mg/kg. Dose related reductions in weight gain were observed for both species. Increased focal lesions and lung discoloration was observed in rats at the 500 mg/kg dose. Significant increases in stomach, kidney and brain relative weights were observed in male rats at 150 mg/kg, with testis relative weight increase at the high dose. Female rats had significantly increased stomach, liver, kidney and brain relative weights at the 150 and 500 mg/kg doses. Microscopic examination showed changes in stomach, liver, lung, spleen, mesenteric and mandibular lymph nodes, kidney and prostrate at the 150 and 500 mg/kg doses. The 50 mg/kg dose produced a 6% increase in relative female stomach weight. The authors concluded that 2-ethylhexanol does not cause tumors in rats (33).

A 90-day subchronic inhalation study of 2-ethylhexanol has also been recently published (34). This study was performed on Wistar rats in accordance with OECD testing guidelines. Groups of 10 rats of each sex were exposed to 2-ethylhexanol vapor at concentrations of 15, 40 and 120 ppm (saturated vapor at 20° C) for 6 hours/day for 90 days. Controls were exposed to air under the same conditions. No substance-related adverse effects were observed for body weight, body weight gain, mortality, organ weights, clinical biochemistry and hematological parameters including clotting time. Cyanide-insensitive palmitoyl-CoA oxidation, a marker for peroxisome proliferation, was not elevated in this study. There were no findings related to the treatment with 2-ethylhexanol either at necropsy or at histological examination. The highest concentration tested under these conditions (120 ppm) was found to be the NOAEL for rats of each sex.

Other Components

The subchronic toxicity of 2-ethyl-1,3-hexanediol was evaluated using groups of rats (five of each sex) given doses of 0, 100, 300, or 1000 mg/kg-day, five days per week over a 29-day period (35). No effects were reported

with regard to mortality, clinical behavior, body weight, feed consumption, or serum chemistry. White blood cell counts, relative liver weights, and relative spleen weights were elevated in females receiving 300 or 1000 mg/kg-day, rats of each sex given 1000 mg/kg, and males given 1000 mg/kg, respectively. Platelet counts were lower in females in the 1000 mg/kg group. The NOAEL was considered to be 100 mg/kg.

The dermal subchronic toxicity of 2-ethyl-1,3-hexanediol has been studied in rats (36). Undiluted test material was applied to the skin of eight-week old Fischer-344-rats at daily doses of 0, 0.5, 2.0, or 4.0 ml/kg, 5 days a week for 9 days or 13 weeks. Selected rats were killed on the last day of the 13-week study, on the tenth day of the 9-day study, or 3 to 5 days or 6 weeks after the last dose of the 13-week study and necropsied. No clinical signs of systemic toxicity or skin irritation were seen in either the 9-day or 13 week study. Slight decreases in body weight gain were reported for the 4.0 ml/kg group males in the 9-day study and for the 4.0 ml/kg rats of each sex in the 13-week study. No treatment related changes in hematology or serum and urinary chemistry were seen. The only treatment-related organ or tissue change identified was a slight increase in relative liver weight ~~seen~~ in the 4.0 ml/kg females after 9 days of treatment and the 4.0 ml/kg males after 13 weeks of treatment. The authors concluded that repeated skin applications of undiluted 2-ethyl-1,3-hexanediol did not cause local skin reactions or systemic toxicity in rats. The slight increases in relative liver weight seen in high dose females in the 9-day study and high dose males in the 13-week study probably reflect an adaptive hypertrophy associated with the metabolism of test substance since these weight increases were not accompanied by any biochemical or morphological evidence of liver injury. The 9-day and 13-week NOAEL was considered to be 4.0 ml/kg.

Repeated administration of 2-ethylhexanal in the diet of rats for three weeks, at about 2,000 mg/kg-day, leads to moderate peroxisome proliferation in the liver as well as hypolipidemia and hepatomegaly (37). An OECD 412 Guideline inhalation study has been conducted on 2-ethylhexanal but the available information giving the results is too limited to draw any conclusions (38).

In summary, available studies of major components of EP-204 have revealed that the materials can be completely metabolized by the body as fatty nutrients with the only effect being an adaptive stimulation of the liver. It is anticipated that all structurally related components will share similar metabolic fates causing liver stimulation (peroxisome proliferation and hypertrophy) as hallmark effects.

Recommendation: No additional repeated-dose studies are recommended. The available data adequately fill the HPV required data element for repeated-dose toxicity.

Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points, one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted on several components of the mixture (indicating low genotoxic hazard) but not on the mixture as a whole to cover either of these endpoints.

Component	Test System	Result	Ref
2-Ethylhexanol	Ames Test [RS]	neg	39
	Ames Tests (multiple)	neg	40, 41, 42, & others
	In vitro CA [RS]	neg	39
	In vitro SCE	neg	39
	HGPRT assay (CHO cells)	neg	43
	Mouse lymphoma assay	neg	44
	Mouse micronucleus (in vivo)	neg	45
	Many others	neg	46
2-Ethyl-1,3-hexanediol	Ames test (multiple)	neg	47, 48, 49
	Gene mutations in CHO cells	neg	47
	SCE in CHO cells	neg	47
	Mouse lymphoma	+/-	48
	CA in CHO cells	+/-	47
	Mouse micronucleus (in vivo)	neg	48
2-Ethylhexenal	Ames test	neg	50, 51
2-Ethylhexanal	Ames test	neg	52
Butyraldehyde	Ames test (multiple)	neg	53, 54, 55, 56
	CA in CHO cells	neg	57
	HGPRT	pos	58
	SCE in CHO cells	pos	57
	SCE in human lymphocytes	neg	59
	Drosophila SLRL test	neg	60, 61

CA= chromosome aberration test, SCE = sister chromatid exchange test, SLRL = sex-linked recessive lethal, [RS] = robust summary prepared

Table 11. Genotoxicity of EP-202 Components

Genetic Toxicology in vivo

Some *in vivo* genotoxicity studies have been conducted on the components of EP-204 and representative results are shown in Table 11. The *in vivo* studies support the *in vitro* data indicating a minimal genotoxic hazard for EP-204.

Recommendation: No additional genetic toxicity testing is recommended as the SIDS requirement for genetic testing is filled by data on the individual components.

Reproductive Toxicity

Although no studies of the EP-204 mixture have been conducted, some of the components have been evaluated and found to have little capacity to produce specific reproductive toxicity. As is the case for most of the health effects studies of EP-204, 2-ethylhexanol is considered to be the most appropriate surrogate for this mixture.

Although a proper guideline-like reproductive toxicity study of 2-ethylhexanol was not found, there are modern 13-week (32) and chronic studies (33) of this material in which the reproductive organs were evaluated. In the case of the 13-week study, gavage dose levels were 0, 25, 125, 250 or 500 mg/kg. The reproductive-organ evaluation showed that aside from an increase in testes weights at the high dose unaccompanied by histological changes, there were no effects on reproductive organs. Results from the chronic study are similar. In addition to these evaluations, there is a dosed-feed developmental toxicity study of 2-ethylhexanol that was conducted in mice at 0, 17, 60 or 194 mg/kg-day (vide post) by the NTP with negative results (65, 66). This combination of lack of effects on reproductive organs combined with a modern developmental toxicity study indicating no developmental effects fulfills the HPV reproductive toxicity endpoint.

Another surrogate chemical for use in assessing the reproductive toxicity of EP-204 is diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol). DEHA is known to be well absorbed by rodents and primates and rapidly converted (both in the gut and after systemic absorption) to 2-ethylhexanol and adipic acid (62). Like 2-ethylhexanol, adipic acid is metabolized via beta-oxidation but metabolized to succinic and acetic acids, and subsequently to other normal intermediary metabolites (63). In a one-generation reproductive study (64), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets at a level of 0, 28, 170, or 1080 mg/kg/day. After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day-36 post partum. Test substance was administered continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. At the highest dose, however, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. The NOAEL and LOAEL for this study were also 170 and 1080 mg/kg/day DEHA [about 120 and 760 mg/kg/day 2-ethylhexanol], respectively. In summary, DEHA administration to male and female rats did not interfere with fertility, even at parentally toxic doses.

Reproductive effects have been adequately assessed through the combination of the negative reproductive and developmental toxicity studies on components of this complex mixture and the subchronic study. Conduct of additional studies on a low-exposure variable mixture would not be a sufficient contribution to warrant use of animals for testing.

Recommendation: No additional reproductive testing is recommended. The available data on components provided sufficient information for informed hazard determination.

Developmental Toxicity

EP-204, as a specific mixture, has not been tested for developmental toxicity but major components have been evaluated and found to have little capacity to produce specific developmental toxicity. As is the case for most of the health effects studies of EP-204, 2-ethylhexanol is considered to be the most appropriate surrogate for this mixture.

The National Toxicology Program has conducted a developmental toxicity study on 2-ethylhexanol in pregnant Swiss mice (65, 66). In this study, groups of 28 pregnant Swiss (CD-1) mice were treated with 2-ethylhexanol (2EH) in feed at 0, 90, 300 or 900 ppm in feed (corresponding to 0, 17, 60, 194 mg/kg-day) in a microencapsulated form. At sacrifice on gestational-day 17, the number of ovarian corpora lutea and uterine implantation sites, including resorptions, and dead or live fetuses, were recorded. Live and dead fetuses were weighed. Live fetuses were sexed and examined for external, visceral and skeletal malformations and variations. No adverse effects on development were reported; however, no maternal toxicity was observed. The NOAEL for developmental and maternal toxicity was > 194 mg/kg.

Dermally administered 2-ethylhexanol was evaluated for developmental toxicity using three groups of 25 pregnant female Fischer 344 rats treated cutaneously with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg-day for 6 hours per day on gestation days 6 through 15 (67). No treatment-related maternal deaths or early pregnancy losses were seen in the treatment groups, but maternal weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals. Exfoliation and crusting were seen at treatment sites at all dose levels and erythema at dose levels of 1.0 and 3.0 ml/kg-day. Low-dose groups, showed an increase in postimplantation loss, decreased litter size, and reduced fetal body weights but this was not observed in the high-dose group; thus a dose-response relationship was not observed for these parameters. There were no significant increases in incidence of malformations in the 2-ethylhexanol groups relative to the sham treatment group. It can be concluded that 2-ethylhexanol has no activity as a developmental toxin by the dermal route in rats. The NOAEL's are considered to be: developmental 3 ml/kg-day, maternal systemic toxicity 1.0 ml/kg-day, and no NOAEL was identified for maternal dermal effects.

As discussed earlier (vide ante), another surrogate chemical for use in assessing the toxicity of EP-204 is diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol). DEHA is rapidly absorbed by rodents and converted to 2-ethylhexanol (68). In a one-generation reproductive study (69), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets (0, 28, 170, or 1080 mg/kg/day). After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day-36 post partum. Test substance was administered continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. At the highest dose, however, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. In summary, DEHA administration to pregnant female rats was associated with only minor manifestations of fetal toxicity at maternally toxic doses. The developmental and maternal NOAEL were 170 mg/kg-day DEHA (~ 120 mg/kg/day 2-ethylhexanol).

2-Ethyl-1,3-hexanediol was studied in an oral-gavage developmental toxicity study sponsored by Kodak (70). In this study, developmental toxicity was evaluated in groups of pregnant Charles River CD rats administered test material by gavage at dose levels of 0, 500, 1000, 2000, or 4000 mg/kg on days 6-15 of gestation. Surviving rats were sacrificed on gestation day 20 for evaluation of the gestational products. One dam at 2000 and seven dams at 4000 mg/kg died on test. Signs of maternal toxicity were observed at 2000 mg/kg and above and included: weakness; dehydration; respiratory problems; abnormal gaits; nasal discharge; porphyrin tears; diarrhea; reduced fecal volume; hypothermia; reduced mean body weights (at all dose levels); significantly increased mean relative liver weights (2000 mg/kg); necrosis of the glandular gastric mucosa; excessive mucus secretion in the cecum; and atrophy of the thymus and adipose tissues. Significantly increased early resorptions were observed at 2000 mg/kg. Fetal malformations were increased for the following at 2000 mg/kg: missing tails; abnormal curvature of the hindlimbs; arthrogyroposis; shortened trunk in the lumbar region; umbilical hernia; and rudimentary (filamentous) tails (at 500, 1000, and 2000 mg/kg). There were no compound-related changes in mean number of corpora lutea, number of implantation sites, viable fetuses/litter, or pre-implantation losses. It is concluded that administration of test material was associated with developmental toxicity at maternally toxic doses. Neither maternal nor developmental NOAELs were identified; however 1000 mg/kg appears to be a developmental NOAEL for major malformations.

2-Ethyl-1,3-hexanediol was also studied in a dermal-administration developmental toxicity study. In this study, developmental toxicity was evaluated in groups of 25 timed-pregnant CD rats administered test material by cutaneous application of undiluted test material at dosages of 1.0, 2.0 and 4.0 ml/kg-day for 6 hr/day under occlusion on gestational days 6-15 inclusive (31). A control group was treated with water using the same exposure regimen. Maternal toxicity was present at 4.0 ml/kg-day (reduced body weight gains and mild skin irritation that were not statistically significant, and statistically significant increased liver weight), and also minimally at 1.0 and 2.0 ml/kg/day (mild skin irritation and slight but significant increase in relative liver weight). At 4.0 ml/kg-day there was one visceral malformation (unilateral hydroureter), increased incidences of three visceral variants (atelectasis, dilated lateral cerebral ventricle, and bilateral dilated ureter), and 13 skeletal variants affecting several skeletal districts. At 2.0 mL/kg/day no malformations were observed, but the incidence of two

visceral variants (dilated lateral cerebral ventricle and bilateral dilated ureter) and one skeletal variant (reduced caudal segments) was increased. The authors concluded that, under the conditions of this study, 2-ethyl-1,3-hexane-1,3-diol is considered a weak developmental toxicant at 4.0 or 2.0 ml/kg-day, and 1 ml/kg-day was a "no-observed effect level" for developmental toxicity.

Both the oral and the dermal developmental toxicity studies of 2-ethyl-1,3-hexanediol are consistent with this material not having developmental toxicity below maternally toxic doses.

In summary, major components of EP-204 have been tested for developmental toxicity and found to produce adverse fetal effects only in the presence of maternal toxicity. Results from these major components are considered to be representative of the developmental toxicity of EP-204 as a mixture.

Recommendation: No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental toxicity of the most volatile component of this material. Conduct of additional studies on a low-exposure variable mixture would not be a significant enough contribution to warrant the use of experimental animals in light of the available information on major components and the composition of EP-204.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that the available information on major components of the mixture EP-204 and on commercial EP-204 itself meet all requirements for physicochemical parameters, fate information, aquatic toxicity and mammalian toxicity. Although the available studies do not meet all the requirements of the current OECD guidelines in all cases, taken together the information provides a reliable hazard assessment.

References

1 Technical Data Sheet for EP-204 2-Ethylhexanol Heavies, dated December 2003 BASF Corporation .

2 Technical Bulletin for EP-204 2-Ethylhexanol Heavies, BASF Corporation, Freeport TX., printed 1997.

3 Sicherheitsdattenblatt fűr Ocooel 800, BASF version of 07.03.2002

4 Estimated from initial boiling point, see robust summary

5 Range of values from most prevalent compounds. Experimental values and EPIWIN estimates. See table of values in text.

6 Based on understanding of reaction chemistry and inspection of chemical structures.

7 BASF AG, Labor Okologie und Umweltanalytic: unpublished report, Prufung der biologischen Abbaubarkeit von Oxooel 800 in CO2 Entwicklungtest. Project Number 96/0418/22/1 7 Feb 1997.

8 Determination of the acute effect of Oxo Oil 800 on the swimming ability of the water flea Daphnia magna STRAUS. Final Report Project Number 96/0418/50/2 BASF AG 10.07.1998.

9 Value from IUCLID 2000 document for 2-Ethylhexanol (CASNO 104-76-7).

10 Huels AG: Report No. FK 1368, 1997 (unpublished) as cited in IUCLID 2000 document for 2-Ethylhexenal (CASNO 645-62-5).

11 Hoechst AG, unveroeffentlichte Untersuchung 79.0533, (1979) zitiert im Hoechst–GDS vom 29.04.1994 as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).

12 Value from IUCLID 2000 document for n-Butanol (CASNO 71-36-3). I

13 BASF AG, Okologie–Labor; unveroeffentl. Untersuchung (1165/87) as cited in IUCLID 2000 document for 2-Ethylhexenal (CASNO 645-62-5).

14 BASF AG, Labor Okologie; unveroeffentlichte Untersuchung, (0423/88) as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).

15 BASF AG(1988), Labor Okologie: Unveroeffentlichte Untersuchung: Algentest vom 16.06.1988 (2/x165/87/t72) as cited in IUCLID 2000 document for 2-Ethylhexenal (CASNO 645-62-5).

16 ECOSAR modeling program, version 0.99f, as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).

17 Clemens, H.P., and K.E. Sneed. Lethal Doses of Several Commercial Chemicals for Fingerling Channel Catfish. U.S.Fish Wildl.Serv.Sci.Rep.Fish.No.316, U.S.D.I., Washington, D.C. 1959. Ac cited in EPA ECOTOX Data Base.

18 Laboratory Report, BASF Toxikologie, Study of the Acute Oral Toxicity to Rats. Substance 84/44, Oxool 800. 30 August 1984.

19 J. Amer. Coll. Toxicol 13(6):418-436 1994

20 Albrow PW, The metabolism of 2-ethylhexanol in rats. Xexnbiotica 5: 625-636 (1975)

21 Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. 3889

22 Frantz SW, Grosse CM. Tallant MJ, Ballantyne B. Pharmacokinetics of 2-ethyl-1,3-hexanediol: I. Systemic disposition following single intravenous doses in male Fischer 344 rats. Drug Metab Dispos; 19 (5). 1991. 881-888.

23 Anonymous. 2-Ethylhexanal. Toxikologische Bewertung. Heidelberg, Berufsgenossenschaft der chemischen Industrie Vol:113 (1989) 9 p

24 Journal of Industrial Hygiene and Toxicology.26:269,1944 as cited in RTECS.

25 Hazardous Substance Databank record for 2-Ethylhexenal. Record # 1716 update of 3/5/2003.

26 2-Ethylhexanol. Toxikologische Bewertung. Heidelberg, Berufsgenossenschaft der chemischen Industrie Vol:114 (1995)

27 Study of Oxoel 800 in an acute inhalation risk test (rats). BASF 84/44 30 May 1984.

28 Patty's Industrial Hygiene and Toxicology, Fourth Edition Vol II 1993 page 292.

29 Chemopetrol, MSDS sheet for CASNO 68609-68-7. 2-Ethylhexanol-heavy parts, revised 11.11.2002.

30 Toxicology of Drugs and Chemicals," Deichmann, W.B., New York, Academic Press., 1969 p.699 1969 as cited in RTECS.

31 Neeper-Bradley TL,Fisher LC, Butler BL, Ballantyne B Evaluation of the developmental toxicity potential of 2-ethyl-1,3-hexanediol in the rat by cutaneous application. J Toxicol Cutaneous Ocul Toxicol 1994;13(3):203-14

32 Astill BD, Deckardt K, Gembardt C, Gingell R, Guest D, Hodgson JR, Mellert W, Murphy SR, Tyler TR. Prechronic toxicity studies on 2-ethylhexanol in F334 rats and B6C3F1 mice. Fundam Appl Toxicol. 1996 29:31-9.

33 Astill BD ; Gingell R ; Guest D ; Hellwig J ; Hodgson JR ; Kuettler K ; Mellert W ; Murphy SR ; Sielken RL Jr; Tyler TR Oncogenicity Testing of 2-Ethylhexanol in Fischer 344 Rats and B6C3F1 Mice. Fundamental and Applied Toxicology, 1996, 31: 29-41.

34 Klimisch H-J, Deckardt K, Gembardt C, Hildebrand B. Subchronic Inhalation Toxicity Study of 2-Ethylhexanol Vapour in Rats. Food And Chemical Toxicology; 36 (3). 1998. 165-168.

35 Eastman Kodak TCSA 8(e) submission: A four week oral toxicity study of 2-ethyl-1,3-haxanediol in the rat TSCA Sect. 8E Rec 02/06/89 EPA/OTS; Doc #89-890000193

36 Van Miller JP, Losco PE, Neptun DA, Ballantyne B. Repeated Exposure Toxicity of 2-Ethyl-1,3-hexanediol by Cutaneous Applications to the Rat for 9 and 90 Days. Veterinary and Human Toxicology, 1995 Vol. 37: 33-36.

37 As cited in: 2-Ethylhexanal. Toxikologische Bewertung. Heidelberg, Berufsgenossenschaft der chemischen Industrie Vol:113 (1989) 9 p

38 See ECB IUCLID-2000 Document for 2-Ethylhexanal for limited details of this TNO study.

39 Data found on NTP public database at http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm

40 Huls Report No 87/353, 1987 (unpublished) as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

41 Kirby PE, et al.(1982). Evaluation of di(2–ethylhexyl)phthalate and its major metabolites in the Ames test and L51 78Y mouse lymphoma mutagenicity assay. Environ Mutagen 4, 388–389. as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

42 EPA Document No. 878213941, Microfiche No. OTS0206391 (1984) as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

43 Litton Bionetics Inc. (1985). Evaluation of 2–Ethylhexanol (2–EH) in the CHO/HGPRT forward mutation assay. No.PE–27.O–GT–LB. as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

44 Kirby PE, et al. (1982). Evaluation of di(2–ethylhexyl)phthalate and its major metabolites in the Ames and L51 78Y mouse lymphoma mutagenicity assay. Environ Mutagen 4, 388–389. as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

45 EPA Document No. 86–870001604, Microfiche No. OTS0516185 (1982). ALSO Barber ED, et al. (1985). The Toxicologist 5(1), 211. . as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

46 See ECB IUCLID-2000 document for 2-Ethylhexanol

47 Slesinski RS, Guzzie PJ, Putman DL, Ballantyne B. In Vitro and In Vivo Evaluation of the Genotoxic Potential of 2-Ethyl-1,3-hexanediol. Toxicology, 1988 53:179-198.

48 Short-Term Test Program Sponsored by the Division Of Cancer Etiology, National Cancer Institute, Dr. David Longfellow, Project Officer,P. Y92 (as cited in CCRIS on NLM)

49 National Toxicology Program testing program result.

50 Zeiger,E, Anderson,B, Haworth,S, Lawlor,T And Mortelmans,K; Salmonella Mutagenicity Tests: IV. Results From the Testing of 300 Chemicals; Environ. Mol. Mutagen. 11(Suppl.12):1-158, 1988 as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

51 BASF AG, Abteilung Toxikologie, unveroeffentl. Untersuchung (90/566), 25.11.91 as cited in ECB IUCLID-2000 document for 2-Ethylhexanol.

52 Zeiger E. et al.: Environ. Molec. Mut., Vol. 11, Suppl. 12,1–158 (1988) as cited in ECB IUCLID-2000 document for 2-Ethylhexanal.

53 Sasaki Y. und Endo R.: Mutat. Res., 54, 251–252,(1978) as cited in ECB IUCLID-2000 document for Butyraldehyde

54 Florin I. et al.: Toxicology, 15, 219–232, (1979) as cited in ECB IUCLID-2000 document for Butyraldehyde

55 Pool B.L. und Wiessler M.: Carcinogenesis, 2, 991–997,(1981) as cited in ECB IUCLID-2000 document for Butyraldehyde

56 Mortelmans K. et al.: Environ. Mutagen., 8, Suppl.7, 1–119,(1986) as cited in ECB IUCLID-2000 document for Butyraldehyde

57 Galloway S.M. et al.: Environ. Molecular Mutagen., 10,Suppl.10, 1–35, (1987) as cited in ECB IUCLID-2000 document for Butyraldehyde

58 Brambilla G. et al.: Mutagenesis, 4, 277–279, (1989) as cited in ECB IUCLID-2000 document for Butyraldehyde

59 Obe G. und Beek B.: Drug and Alcohol Dependence, 4, 91–94, (1979) as cited in ECB IUCLID-2000 document for Butyraldehyde

60 Valencia R. et al.: Environ. Mutagen., 7, 325–348, (1985) as cited in ECB IUCLID-2000 document for Butyraldehyde

61 Valencia et al.: cited in Mason J.M. et al.: Env. molec. mutag. 19, 227-234 as cited in ECB IUCLID-2000 document for Butyraldehyde

62 Anonymous. Di-(2-ethylhexyl)adipat. Beratergremium fuer umweltrelevante Altstoffe (BUA) Vol:196 (1997)

63 Clayton, G.D., F.E. Clayton (eds.) Patty's Industrial Hygiene and Toxicology. 4th ed. New York, NY: John Wiley & Sons Inc., 1993-1994. 3587 and Rusoff II et al; Toxicol Appl Pharmacol 2: 316-30 (1960). As cited in NLM Hazardous Ssubstance DataBase record to adipic acid.

64 ICI. 1988b. ICI Central Toxicology Laboratory. Di-(2-ethylhexyl)adipate (DEHA): Fertility study in rats. Report CTL/P/2229 (unpublished study). As cited in IRIS, US EPA.

65 Price CJ; Tyl RW; Marr MC; Myers CB; Morrissey RE; Heindel JJ; Schwetz BA Developmental toxicity evaluation of DEHP metabolites in Swiss mice. Teratology 1991 May;43(5):457

66 Developmental Toxicity of 2-Ethylhexanol (CAS NO. 104-76-7) in CD-1 Swiss Mice NTP Study: TER90029. Abstract available on the NTP web site and the entire report is available from NTIS.

67 Developmental toxicity evaluation of 2-ethylhexanol administered cutaneously to Fischer 344 rats (final report) with attachments and cover letters dated 032189 and 050389, Bushy Run Research Center, EPA/OTS; Doc #86-890000216

68 Anonymous. Di-(2-ethylhexyl)adipat. Beratergremium fuer umweltrelevante Altstoffe (BUA) Vol:196 (1997)

66 ICI. 1988. ICI Central Toxicology Laboratory. Di-(2-ethylhexyl)adipate: Teratogenicity study in the rat. Report CTL/P/2119 (unpublished study). As cited in IRIS, US EPA.

70 Study on the developmental toxicity of 2-ethyl-1,3-hexanediol in rats (final report). EPA/OTS; Doc #89-890000090; TSCA Sect. 8E Rec 02/06/89, TSCATS/312452, NTIS/OTS0516641-1

201-15756

IUCLID

Data Set

Existing Chemical	:	ID: 68609-68-7
CAS No.	:	68609-68-7
Producer related part		
Company	:	BASF Corporation
Creation date	:	30.12.2003
Substance related part		
Company	:	BASF Corporation
Creation date	:	30.12.2003
Status	:	
Memo	:	Prepared by: Toxicology and Regulatory Affairs Freeburg IL 62243 618-538-5280
Printing date	:	24.12.2004
Revision date	:	
Date of last update	:	24.12.2004
Number of pages	:	51
Chapter (profile)	:	Chapter: 1.0.1, 1.2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.3.2, 3.5, 4.1, 4.2, 4.3, 4.4, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.7, 5.8.1, 5.8.2
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.2 SYNONYMS AND TRADENAMES

2.1 MELTING POINT

Value : ca. -62 °C

Remark :
As this material is a variable mixture this must be considered as only an approximation of the actual freezing point for any batch.

Test substance :
EP-204 CASNO 68609-68-7

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
30.12.2003 (6)

2.2 BOILING POINT

Value : ca. 180 - 350 °C at 1013 hPa

Remark :
As this material is a variable mixture this must be considered as only an approximation of the boiling point for any batch.

Test substance :
EP-204 CASNO 68609-68-7

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
02.01.2004 (1)

2.4 VAPOUR PRESSURE

Value : ca. 1 - 5 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year :
GLP :
Test substance :

Method :
The vapor pressure for the mixture is estimated using the mean of the Antoine & Grain methods as calculated using the MPBPWIN v1.40 program found in EPIWIN 3.05. The initial boiling point and the final boiling point are the only input parameters this estimate is based on, as the program is insensitive to structure if a determined boiling point is an input. Likewise, the program is insensitive to melting point when calculating VPs for liquids.

The structure for 2-ethylhexyl-1,3-diol was entered to provide a reference value for one of the pure components.

As this is a variable mixture, the initial and final boiling point values are also variable

Result :

Experimental Database Structure Match:
Name : 2-ETHYL-1,3-HEXANDIOL
CAS Num : 000094-96-2
Exp MP (deg C): -40
Exp BP (deg C): 244
Exp VP (mm Hg): 3.00E-03 (extrapolated)
Exp VP (deg C): 25
Exp VP ref : BLAINE,RL (1976)

SMILES : CCCC(O)C(CC)CO
CHEM : EP-204
MOL FOR: C8 H18 O2
MOL WT : 146.23

+++++++BASED ON INITIAL BP OF 180 deg C

---------- SUMMARY MPBPWIN v1.40 ----------

Boiling Point: 242.50 deg C (Adapted Stein and Brown Method)

Melting Point: -1.60 deg C (Adapted Joback Method)
Melting Point: 27.93 deg C (Gold and Ogle Method)
Mean Melt Pt : 13.17 deg C (Joback; Gold,Ogle Methods)
Selected MP: 13.17 deg C (Mean Value)

Vapor Pressure Estimations (25 deg C):
(Using BP: 180.00 deg C (user entered))
(MP not used for liquids)
VP: 0.197 mm Hg (Antoine Method)
VP: 0.157 mm Hg (Modified Grain Method)
VP: 1.37 mm Hg (Mackay Method)
Selected VP: 0.177 mm Hg (Mean of Antoine & Grain methods)

+++++++++ BASED ON FINAL BP OF 350 dec C
---------- SUMMARY MPBPWIN v1.40 ----------
Boiling Point: 242.50 deg C (Adapted Stein and Brown Method)
Melting Point: -1.60 deg C (Adapted Joback Method)
Melting Point: 27.93 deg C (Gold and Ogle Method)
Mean Melt Pt : 13.17 deg C (Joback; Gold,Ogle Methods)
Selected MP: 13.17 deg C (Mean Value)

Vapor Pressure Estimations (25 deg C):
(Using BP: 350.00 deg C (user entered))
(MP not used for liquids)
VP: 9.62E-007 mm Hg (Antoine Method)
VP: 2.5E-006 mm Hg (Modified Grain Method)
VP: 0.000262 mm Hg (Mackay Method)
Selected VP: 2.5E-006 mm Hg (Modified Grain Method)

Test substance :

EP-204 CASNO 68609-68-7

Conclusion

The calculated vapor pressure for this mixture, assuming it is a pure material of boiling point 180 deg C, is approximately 0.2 mm Hg. As this is a variable mixture, a specific VP cannot be stated. It is concluded that giving the VP as a range of 0.1 to 2 hPa is a conservative yet realistic estimate.

Reliability : (2) valid with restrictions

Estimates using an acceptable method are assigned a reliability score of 2.

Flag : Critical study for SIDS endpoint

02.01.2004 (15) (18)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : at °C
pH value :
Method :
Year :
GLP :
Test substance : other TS

Method :

Octanol water partition coefficients for the major components of EP-202 were obtained through the KOWWIN program (v1.66) by entering the structure of the component into the program using the SMILES code. These codes are listed in the results section. Where there was an experimental value found in the database associated with the program, that value was accepted. Where an experimental value was not found the program estimate was accepted.

Result :

KOWWIN Program (v1.66) Results:

SMILES : CCCCC(CC)CO
CHEM : 2-Ethylhexanol
MOL FOR: C8 H18 O1
MOL WT : 130.23
Log Kow(version 1.66 estimate): 2.73

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	5	-CH2- [aliphatic carbon]	0.4911	2.4555
Frag	1	-CH [aliphatic carbon]	0.3614	0.3614
Frag	1	-OH [hydroxy, aliphatic attach]	-1.4086	-1.4086
Const		Equation Constant		0.2290
			Log Kow =	2.7319

SMILES : CCCC=C(CC)C=O
CHEM : 2-Ethylhexenal
MOL FOR: C8 H14 O1
MOL WT : 126.20
Log Kow(version 1.66 estimate): 2.62

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	3	-CH2- [aliphatic carbon]	0.4911	1.4733
Frag	2	=CH- or =C< [olefinc carbon]	0.3836	0.7672
Frag	1	-CHO [aldehyde, aliphatic attach]	-0.9422	-0.9422
Const		Equation Constant		0.2290
			Log Kow =	2.6219

SMILES : CCCCC(CC)C=O
CHEM : 2-Ethylhexanal
MOL FOR: C8 H16 O1
MOL WT : 128.22
Log Kow(version 1.66 estimate): 2.71

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	4	-CH2- [aliphatic carbon]	0.4911	1.9644
Frag	1	-CH [aliphatic carbon]	0.3614	0.3614
Frag	1	-CHO [aldehyde, aliphatic attach]	-0.9422	-0.9422
Const		Equation Constant		0.2290
			Log Kow =	2.7072

SMILES : CCCCO
CHEM : n-Butanol
MOL FOR: C4 H10 O1
MOL WT : 74.12
Log Kow(version 1.66 estimate): 0.84
Experimental Database Structure Match:
Name : 1-Butanol
CAS Num : 000071-36-3
Exp Log P: 0.88
Exp Ref : Hansch,C et al. (1995)

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	3	-CH2- [aliphatic carbon]	0.4911	1.4733
Frag	1	-OH [hydroxy, aliphatic attach]	-1.4086	-1.4086
Const		Equation Constant		0.2290
			Log Kow =	0.8410

SMILES : CCCC(O)C(CC)CO
CHEM : 2-Ethyl-1,3-hexanediol
MOL FOR: C8 H18 O2
MOL WT : 146.23
Log Kow(version 1.66 estimate): 1.60

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	4	-CH2- [aliphatic carbon]	0.4911	1.9644
Frag	2	-CH [aliphatic carbon]	0.3614	0.7228
Frag	2	-OH [hydroxy, aliphatic attach]	-1.4086	-2.8172
Factor	1	Multi-alcohol correction	0.4064	0.4064
Const		Equation Constant		0.2290
			Log Kow =	1.6000

SMILES : CCCC(OC(=O)CCC)C(CC)COC(=O)CCC
CHEM : 2-Ethylhexyl-1,3-dibutyrate
MOL FOR: C16 H30 O4
MOL WT : 286.42
Log Kow(version 1.66 estimate): 5.17

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	4	-CH3 [aliphatic carbon]	0.5473	2.1892
Frag	8	-CH2- [aliphatic carbon]	0.4911	3.9288
Frag	2	-CH [aliphatic carbon]	0.3614	0.7228
Frag	2	-C(=O)O [ester, aliphatic attach]	-0.9505	-1.9010
Const		Equation Constant		0.2290
			Log Kow =	5.1688

SMILES : CCCC(=O)OCCCC
CHEM : N-butyl-n-butyrate
MOL FOR: C8 H16 O2
MOL WT : 144.22
Log Kow(version 1.66 estimate): 2.83

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	5	-CH2- [aliphatic carbon]	0.4911	2.4555
Frag	1	-C(=O)O [ester, aliphatic attach]	-0.9505	-0.9505
Const		Equation Constant		0.2290
			Log Kow =	2.8286

SMILES : CCCC=O
CHEM : N-butyraldehyde
MOL FOR: C4 H8 O1
MOL WT : 72.11
Log Kow(version 1.66 estimate): 0.82

Experimental Database Structure Match:
Name : Butyraldehyde
CAS Num : 000123-72-8
Exp Log P: 0.88
Exp Ref : Hansch,C et al. (1995)

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	2	-CH2- [aliphatic carbon]	0.4911	0.9822
Frag	1	-CHO [aldehyde, aliphatic attach]	-0.9422	-0.9422
Const		Equation Constant		0.2290
			Log Kow =	0.8163

SMILES : CCCCC(CC)CC(CC)CO
CHEM : 2,4-Diethyloctane-1-ol
MOL FOR: C12 H26 O1
MOL WT : 186.34

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	3	-CH3 [aliphatic carbon]	0.5473	1.6419
Frag	7	-CH2- [aliphatic carbon]	0.4911	3.4377
Frag	2	-CH [aliphatic carbon]	0.3614	0.7228
Frag	1	-OH [hydroxy, aliphatic attach]	-1.4086	-1.4086
Const		Equation Constant		0.2290
			Log Kow =	4.6228

SMILES : CCCC(O)C(CC)CC(CC)CO
CHEM : 2,4-Diethyloctane-1,5-diol
MOL FOR: C12 H26 O2
MOL WT : 202.34

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	3	-CH3 [aliphatic carbon]	0.5473	1.6419
Frag	6	-CH2- [aliphatic carbon]	0.4911	2.9466
Frag	3	-CH [aliphatic carbon]	0.3614	1.0842
Frag	2	-OH [hydroxy, aliphatic attach]	-1.4086	-2.8172
Factor	1	Multi-alcohol correction	0.4064	0.4064
Const		Equation Constant		0.2290
			Log Kow =	3.4909

SMILES : CCC(CO)C(CCC)C(CO)CC
CHEM : 2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol)
MOL FOR: C12 H26 O2
MOL WT : 202.34

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	3	-CH3 [aliphatic carbon]	0.5473	1.6419
Frag	6	-CH2- [aliphatic carbon]	0.4911	2.9466
Frag	3	-CH [aliphatic carbon]	0.3614	1.0842
Frag	2	-OH [hydroxy, aliphatic attach]	-1.4086	-2.8172
Factor	1	Multi-alcohol correction	0.4064	0.4064
Const		Equation Constant		0.2290
			Log Kow =	3.4909

SMILES : CCC(CO)CC(CC)C(CCC)C(CO)CC
CHEM : 2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)
MOL FOR: C16 H34 O2
MOL WT : 258.45

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	4	-CH3 [aliphatic carbon]	0.5473	2.1892
Frag	8	-CH2- [aliphatic carbon]	0.4911	3.9288
Frag	4	-CH [aliphatic carbon]	0.3614	1.4456
Frag	2	-OH [hydroxy, aliphatic attach]	-1.4086	-2.8172
Factor	1	Multi-alcohol correction	0.4064	0.4064
Const		Equation Constant		0.2290
			Log Kow =	5.3818

SMILES : CCCCC(CC)COCCCC
CHEM : 2-Ethylhexyl-n-butyl ether
MOL FOR: C12 H26 O1
MOL WT : 186.34

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	3	-CH3 [aliphatic carbon]	0.5473	1.6419
Frag	8	-CH2- [aliphatic carbon]	0.4911	3.9288
Frag	1	-CH [aliphatic carbon]	0.3614	0.3614
Frag	1	-O- [oxygen, aliphatic attach]	-1.2566	-1.2566
Const		Equation Constant		0.2290
			Log Kow =	4.9045

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Conclusion :

The following values were found for log Kow

COMPONENT********	**log Kow**
2-Ethylhexanol	2.73 c
2-Ethylhexenal	2.62 c
2-Ethylhexanal	2.71 c
N-butanol	0.88 e
2-Ethyl-1,3-hexanediol	1.60 c
2-Ethylhexyl-1,3-dibutyrate	5.17 c
2,4-Diethyloctane-1-ol	4.62 c
2,4-Diethyloctane-1,5-diol	3.49 c
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol	3.49 c
2,4,6-Triethyl-3-propylheptane-1,7-diol	4.89 c
N-butyl-n-butyrate	2.83 c
N-butyraldehyde	-0.48 e

e = experimental
c = calculated

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
24.12.2004 (20)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Method :

Water solubility estimates and experimental values for the major components of EP-202 were obtained through the WSKOW program (v1.40) by entering the structure of the component into the program using the SMILES code. These codes are listed in the results section. Where there was an experimental value found in the database associated with the program, that value was accepted. Where an experimental value was not found the program estimate was accepted.

The following formula was used by the program to estimate the water solubility:

Log S (mol/L) = 0.796 - 0.854 log Kow - 0.00728 MW + Correction

The only Correction Value that was applied was for the non-diol aliphatic alcohols.

Alcohol, aliphatic 0.510

Result :

The following results were obtained for water solubility:

COMPONENT	***SMILES****	***Kow***	Water Sol **(mg/L)**
2-Ethylhexanol	CCCCC(CC)CO	2.73c	880e
2-Ethylhexenal	CCCC=C(CC)C=O	2.62c	548e
2-Ethylhexanal	CCCCC(CC)C=O	2.71c	400e
n-Butanol	CCCCO	0.88e	63200e
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	1.60c	4200e
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	5.17c	0.57e
n-Butyl-n-butyrate	CCCC(=O)OCCCC	2.83c	309c
n-Butyraldehyde	CCCC=O	-0.48e	2385e
2,4-Diethyloctane-1-ol	CCCCC(CC)CC(CC)CO	4.62c	18.7c
2,4-Diethyloctane-1,5-diol	CCCC(O)C(CC)CC(CC)CO	3.49c	44.4c
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol)	CCC(CO)C(CCC)C(CO)CC	3.49c	44.4c
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CCC(CO)CC(CC)C(CCC)C(CO)CC	4.89c	1.69c
2-Ethylhexyl-butyl ether	CCCCC(CC)COCCCC	4.90c	3.32c

e = experimental
c = calculated

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Conclusion :

Water solubility varies for components of EP-204 from less than 1 mg/L to greater than 1000 mg/L

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
24.12.2004 (20)

3.1.1 PHOTODEGRADATION

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight

Method :

The structure of the various identified and anticipated components was initially examined to determine if there was a chromophore that could absorb light energy at wavelengths above 295 um. As none of the conjugated systems was likely to absorb light in the appropriate wavelength and as the material is basically colorless, it was assumed that direct photolysis would be unimportant to the fate of the test material.

To estimate indirect photolysis, the various major components were examined using the APOWIN (1.90) program found in EPIWIN. This program estimates the reaction rate of the molecule with hydroxyl radical based on its structural components that are reactive with atmospheric hydroxyl radical. An overall rate constant is estimated and a search is conducted for materials with experimentally determined rate constants. The program then calculates an approximate atmospheric half-life using a (used defined) 12-hour day and hydroxyl radical concentration.

Olefinic compounds were also evaluated for reactivity with atmospheric ozone. Some components were judged to be ozone reactive but the contribution of this sensitizer was negligible as compared to hydroxyl radical and was ignored in constructing the table.

This analysis was conducted for each of the identified major components and structures representative of the various classes of components. Under environmental conditions of essentially infinite dilution, each component is considered to photodegrade independently of the other components in the mixture.

Result :

AOP Program (v1.90) Results:
==========
SMILES : CCCC=C(CC)C=O
CHEM : 2-Ethylhexenal
MOL FOR: C8 H14 O1
MOL WT : 126.20

---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 20.4442 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 29.5460 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 49.9902 E-12 cm3/molecule-sec
HALF-LIFE = 0.214 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 2.568 Hrs

---------- SUMMARY (AOP v1.90): OZONE REACTION ----
OVERALL OZONE Rate Constant = 1.183000 E-17 cm3/molecule-sec
HALF-LIFE = 0.969 Days (at 7E11 mol/cm3)
HALF-LIFE = 23.249 Hrs

Experimental Database: NO Structure Matches

AOP Program (v1.90) Results:
==========
SMILES : CCCCC(CC)C=O
CHEM : 2-Ethylhexanal
MOL FOR: C8 H16 O1
MOL WT : 128.22
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 33.9806 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 33.9806 E-12 cm3/molecule-sec
HALF-LIFE = 0.315 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 3.777 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

AOP Program (v1.90) Results:
==========
SMILES : CCCCO
CHEM : n-Butanol
MOL FOR: C4 H10 O1
MOL WT : 74.12
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 6.7500 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.1400 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 6.8900 E-12 cm3/molecule-sec
HALF-LIFE = 1.552 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 18.629 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******

(ONLY Olefins and Acetylenes are Estimated)

Experimental Database Structure Match:
Chem Name : 1-Butanol
CAS Number: 000071-36-3
Exper OH rate constant : 8.57 E-12 cm3/molecule-sec
Exper OH Reference: KWOK,ESC & ATKINSON,R (1994)
Exper Ozone rate constant: --- cm3/molecule-sec
Exper NO3 rate constant : --- cm3/molecule-sec

SMILES : CCCC(O)C(CC)CO
CHEM : 2-Ethyl-1,3-hexanediol
MOL FOR: C8 H18 O2
MOL WT : 146.23
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 21.9488 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.2800 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 22.2288 E-12 cm3/molecule-sec
HALF-LIFE = 0.481 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 5.774 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

==========
SMILES : CCCC(OC(=O)CCC)C(CC)COC(=O)CCC
CHEM : 2-Ethylhexyl-1,3-dibutyrate
MOL FOR: C16 H30 O4
MOL WT : 286.42
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 17.5340 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 17.5340 E-12 cm3/molecule-sec
HALF-LIFE = 0.610 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 7.320 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

SMILES : CCCC(=O)OCCCC
CHEM : n-butyl-n-butyrate
MOL FOR: C8 H16 O2
MOL WT : 144.22
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 6.2395 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 6.2395 E-12 cm3/molecule-sec
HALF-LIFE = 1.714 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 20.571 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database Structure Match:
Chem Name : n-Butyl butyrate
CAS Number: 000109-21-7
Exper OH rate constant : 10.6 E-12 cm3/molecule-sec
Exper OH Reference: ATKINSON,R (1989)
Exper Ozone rate constant: --- cm3/molecule-sec
Exper NO3 rate constant : --- cm3/molecule-sec

HALF-life Based on Experimental Rate Constant: 12.1 hours

==========
SMILES : CCCC=O
CHEM : n-butyraldehyde
MOL FOR: C4 H8 O1
MOL WT : 72.11
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 25.4314 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 25.4314 E-12 cm3/molecule-sec
HALF-LIFE = 0.421 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 5.047 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database Structure Match:
Chem Name : Butanal
CAS Number: 000123-72-8
Exper OH rate constant : 23.5 E-12 cm3/molecule-sec

Exper OH Reference: ATKINSON,R (1985)
Exper Ozone rate constant: --- cm3/molecule-sec
Exper NO3 rate constant : --- cm3/molecule-sec

AOP Program (v1.90) Results:
==========
SMILES : CCCCC(CC)CC(CC)CO
CHEM : 2,4-Diethyloctane-1-ol
MOL FOR: C12 H26 O1
MOL WT : 186.34
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 19.4285 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.1400 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 19.5685 E-12 cm3/molecule-sec
HALF-LIFE = 0.547 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 6.559 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

AOP Program (v1.90) Results:
==========
SMILES : CCCC(O)C(CC)CC(CC)CO
CHEM : 2,4-Diethyloctane-1,5-diol
MOL FOR: C12 H26 O2
MOL WT : 202.34
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 28.2880 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.2800 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 28.5680 E-12 cm3/molecule-sec
HALF-LIFE = 0.374 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 4.493 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

SMILES : CCCCC(CC)CO
CHEM : 2-Ethylhexanol
MOL FOR: C8 H18 O1
MOL WT : 130.23
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 13.0893 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.1400 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 13.2293 E-12 cm3/molecule-sec
HALF-LIFE = 0.809 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 9.702 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

SMILES : CCC(CO)C(CCC)C(CO)CC
CHEM : 2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol-2)
MOL FOR: C12 H26 O2
MOL WT : 202.34
--------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 24.2333 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.2800 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 24.5133 E-12 cm3/molecule-sec
HALF-LIFE = 0.436 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 5.236 Hrs
------- SUMMARY (AOP v1.90): OZONE REACTION ----------

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

CHEM : 2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)
MOL FOR: C15 H32 O2
MOL WT : 244.42
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 28.7487 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.2800 E-12 cm3/molecule-sec

Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 29.0287 E-12 cm3/molecule-sec
HALF-LIFE = 0.368 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 4.422 Hrs
---------- SUMMARY (AOP v1.90): OZONE REACTION ----

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

AOP Program (v1.90) Results:
==========
SMILES : CCCCC(CC)COCCCC
CHEM : 2-Ethylhexyl-n-butyl ether
MOL FOR: C12 H26 O1
MOL WT : 186.34
--------- SUMMARY (AOP v1.90): HYDROXYL RADICALS --------
Hydrogen Abstraction = 35.0835 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 35.0835 E-12 cm3/molecule-sec
HALF-LIFE = 0.305 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 3.658 Hrs

----- SUMMARY (AOP v1.90): OZONE REACTION ----------

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Conclusion :

Estimated or experimental rate constants for reaction with hydroxyl radical and predicted half-lives in air are shown in the table. Expected half-lives range from 2.6 hours to 18.6 hours assuming a 12-hhour day and a concentration of 1,500,000 hydroxyl radicals per cubic centimeter.

The material is not considered persistent in the atmosphere.

COMPONENT	SMILES	Rate K*	t1/2(h)
2-Ethylhexanol	CCCCC(CC)CO	13.2	9.7
2-Ethylhexenal	CCCC=C(CC)C=O	50.0	2.6
2-Ethylhexanal	CCCCC(CC)C=O	34.0	3.8
n-Butanol	CCCCO	6.9	18.6
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	22.2	5.8
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	17.5	7.3
n-butyl-n-butyrate	CCCC(=O)OCCCC	10.6	12.1
n-butyraldehyde	CCCC=O	25.4	5.0
2,4-Diethyloctane-1-ol	CCCCC(CC)CC(CC)CO	19.6	6.6
2,4-Diethyloctane-1,5-diol	CCCC(O)C(CC)CC(CC)CO	28.6	4.5
2-Ethyl-3-propyl-4-hydroxy-methylhexan-1-ol (C12)	CCC(CO)C(CCC)C(CO)CC	24.5	5.2
2,4,6-Triethyl-3-propyl-heptane-1,7-diol (C-16)	CC(CO)CC(CC)C(CCC)C(CO)CC	29.3	4.4
2-Ethylhexyl-butyl ether	CCCC(CC)COCCCC	35.1	3.7

* Rate constants in units of x exp12 cm/molec-sec
Half-life in units of hours

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method are assigned a reliability of 2

Flag : Critical study for SIDS endpoint

10.02.2004 (2)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : > 1 year at 25 °C
t1/2 pH9 : at °C
Deg. product :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method :

Under aqueous-solution conditions where essentially infinite dilution conditions can be assumed, water stability of the individual components can be estimated based on their chemical properties. Most components of EP-204 have no hydrolysable group and are therefore considered resistant to hydrolysis. These are:

* Aliphatic alcohols
* Aliphatic aldehydes
* Aliphatic carboxylic acids
* Alkenes
* Aliphatic ethers

The following components have hydrolysable groups:

* Aliphatic acetals
* Aliphatic esters

The stability of the aliphatic esters has been estimated using the HYDROWIN Program (v1.67) found in the EPIWIN software (see following

robust summaries).

Stability of acetals cannot be estimated using the EPIWIN software and no definitive information was located on the water stability of these medium to long-chain acetals. As simple acetals are typically resistant to hydrolysis at neutral pH (Vollhardt, K. Peter, Organic Chemistry, WH Freeman and Company, New York 1987, p 640) and as the acetals are a minor component of EP-204, their contribution to the water stability is minimal and they are estimated based on the know chemistry of acetals, to have a a half-life greater than one year.

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Conclusion :

EP-204 is considered to be relativley water stable.

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method as assigned a reliability of 2

Flag : Critical study for SIDS endpoint

27.01.2004 (13)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : ca. 4.1 year at 25 °C
t1/2 pH9 : ca. 15 day(s) at 25 °C
Deg. product :
Method :
Year :
GLP : no
Test substance : other TS

Method :

Estimation of the hydrolysis of ester components of EP-204 was conducted using the HYDROWIN (ver 1.67) program found in EPIWIN 3.05. The methodology for prediction of hydrolysis rates was developed for the U.S. Environmental Protection Agency and is described in the document: Mill,T., Haag,W., Penwell, P., Pettit, T. and Johnson, H. "Environmental Fate and Exposure Studies Development of a PC-SAR for Hydrolysis: Esters, Alkyl Halides and Epoxides". EPA Contract No. 68-02-4254. Menlo Park, CA: SRI International (1987).

The program calculates the base-catalyzed rate constant for esters using the following equation:

log Kb = 0.92Es{R1} + 0.31Es{R2} + 2.16 sigma*{R1} + 2.30 sigma*{R2} + 2.10 sigmaX{R1} + 1.25 sigmaX{R2} + 2.67

where R1 and R2 designate the carbon shins, Es is the steric factor at the designated position, sigma* is the Taft constant at the designated position, and sigmaX is the Hammett constant at the designated position.

The overall hydrolysis rate constant is equal to the acid-catalyzed plus the base-catalyzed plus the neutral hydrolysis rate constants. In the case of esters it is established that for most esters the base reaction rate dominates by a wide margin and acid and neutral hydrolysis can largely be ignored.

Result :

SMILES : CCCC(=O)OCCCC
CHEM : n-butyl-n-butyrate
MOL FOR: C8 H16 O2
MOL WT : 144.

----- HYDROWIN v1.67 Results ----------

ESTER: R1-C(=O)-O-R2 R1: n-Propyl-

R2: n-Butyl-

Kb hydrolysis at atom # 4: 5.317E-002 L/mol-sec

Total Kb for pH > 8 at 25 C: 5.317E-002 L/mol-sec
Kb Half-Life at pH 8: 150.863 days
Kb Half-Life at pH 7: 4.130 years

Test substance :

n-Butyl-n-butyrate
SMILES: CCCC(=O)OCCCC
Component of EP204

Conclusion :

This material is stable to hydrolysis at pH levels near neutrality having a predicted half-life in the range of 4 years.

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method as assigned a reliability of 2

Flag : Critical study for SIDS endpoint

01.02.2004 (12)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : ca. 6.2 year at 25 °C
t1/2 pH9 : ca. 22.6 day(s) at 25 °C
Deg. product :
Method : other (calculated)
Year :
GLP : no
Test substance : other TS

Method :

Estimation of the hydrolysis of ester components of EP-204 was conducted using the HYDROWIN (ver 1.67) program found in EPIWIN 3.05. The methodology for prediction of hydrolysis rates was developed for the U.S. Environmental Protection Agency and is described in the document: Mill,T., Haag,W., Penwell, P., Pettit, T. and Johnson, H. "Environmental Fate and Exposure Studies Development of a PC-SAR for Hydrolysis: Esters, Alkyl Halides and Epoxides". EPA Contract No. 68-02-4254. Menlo Park, CA: SRI International (1987).

The program calculates the base-catalyzed rate constant for esters using the following equation:

log Kb = 0.92Es{R1} + 0.31Es{R2} + 2.16 sigma*{R1} + 2.30 sigma*{R2} + 2.10 sigmaX{R1} + 1.25 sigmaX{R2} + 2.67

where R1 and R2 designate the carbon chains, Es is the steric factor at the

designated position, sigma* is the Taft constant at the designated position, and sigmaX is the Hammett constant at the designated position.

The overall hydrolysis rate constant is equal to the acid-catalyzed plus the base-catalyzed plus the neutral hydrolysis rate constants. In the case of esters it is established that for most esters the base reaction rate dominates by a wide margin and acid and neutral hydrolysis can largely be ignored.

In the case of these n-butyl esters, the Taft and Hammett constants were not available for both positions so the program substituted the values using surrogates.

Result :

SMILES : CCCC(OC(=O)CCC)C(CC)COC(=O)CCC
CHEM : 2-Ethylhexyl-1,3-dibutyrate
MOL FOR: C16 H30 O4
MOL WT : 286.42
---------- HYDROWIN v1.67 Results ----------

NOTE: Fragment(s) on this compound are NOT available from the fragment
library. Substitute(s) have been used!!! Substitute R1, R2, R3, or R4 fragments are marked with double astericks "**".

ESTER: R1-C(=O)-O-R2 R1: n-Propyl-
** R2: -CH(Me)(t-Bu)
Kb hydrolysis at atom # 6: 1.455E-003 L/mol-sec

ESTER: R1-C(=O)-O-R2 R1: n-Propyl-
** R2: iso-Butyl-
Kb hydrolysis at atom # 16: 3.416E-002 L/mol-sec

Total Kb for pH > 8 at 25 deg C : 3.561E-002 L/mol-sec
Kb Half-Life at pH 8: 225.252 days
Kb Half-Life at pH 7: 6.167 years

Test substance :

2-Ethylhexyl-1,3-dibutyrate
SMILES : CCCC(OC(=O)CCC)C(CC)COC(=O)CC
Component of EP-204

Conclusion :

This material is stable to hydrolysis at pH levels near neutrality having a predicted half-life in the range of 6 years

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method as assigned a reliability of 2

Flag : Critical study for SIDS endpoint
27.01.2004 (3)

3.3.2 DISTRIBUTION

Media : other: Air, water, soil and sediment
Method : Calculation according Mackay, Level III
Year : 2003

Method :

Theoretical Distribution (Fugacity) of EP-204 in the environment was estimated using the MacKay EQC level III model with standard defaults in EPIWIN v 3.05 using equal releases to water, soil and air (EPIWN default) as the means of entry into the environment. The approach used was to take the nine materials represented in the in the preparation at greater than 1% and individually determine their fugacity assuming that one component will not greatly affect the distribution of the other. As the measured vapor pressure of EP-2042 is a function of the partial pressures of each component, it is more appropriate to use the EPIWIN predicted vapor pressure for each component in the calculation. Likewise, individual predicted values for log Kow, Koc, and half-lives were utilized. The biodegradation half-lives that were utilized were EPIWIN generated but were evaluated for consistency with the known biodegradability of the preparation and found to be representative.

Result :

```
Level III Fugacity Model (Full-Output):
=======================================
  Chem Name   : 2-Ethylhexenal
  Molecular Wt: 126.2
  Henry's LC  : 0.000488 atm-m3/mole (Henrywin program)
  Vapor Press : 0.463 mm Hg  (Mpbpwin program)
  Log Kow     : 2.62  (Kowwin program)
  Soil Koc    : 171  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       0.937           4.21         0
   Water     98.4            360          1000
   Soil      0.00879         360          0
   Sediment  0.614           1.44e+003    0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
   Air       4.01e-012    342         20.7        34.2        2.07
   Water     4.21e-009    419         218         41.9        21.8
   Soil      9.48e-013    0.0374      0           0.00374     0
   Sediment  2.57e-009    0.653       0.0272      0.0653      0.00272

   Persistence Time: 221 hr
   Reaction Time:    291 hr
   Advection Time:   927 hr
   Percent Reacted:  76.1
   Percent Advected: 23.9

   Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
      Air:      4.207
      Water:    360
      Soil:     360
      Sediment: 1440
        Biowin estimate: 3.241  (weeks       )
```

```
  Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004


=======================================
  Chem Name   : 2-Ethylhexanal
  Molecular Wt: 128.22
  Henry's LC  : 0.000759 atm-m3/mole (Henry database)
  Vapor Press : 2.18 mm Hg  (Mpbpwin program)
  Log Kow     : 2.71  (Kowwin program)
  Soil Koc    : 210  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       1.81            7.56         0
   Water     97.5            360          1000
   Soil      0.0149          360          0
   Sediment  0.688           1.44e+003    0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
   Air       7.34e-012    353         38.5        35.3        3.85
   Water     6.14e-009    400         208         40          20.8
   Soil      1.95e-012    0.0612      0           0.00612     0
   Sediment  3.59e-009    0.705       0.0293      0.0705      0.00293

   Persistence Time: 213 hr
   Reaction Time:    282 hr
   Advection Time:   865 hr
   Percent Reacted:  75.4
   Percent Advected: 24.6

   Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
      Air:      7.555
      Water:    360
      Soil:     360
      Sediment: 1440
        Biowin estimate: 3.236  (weeks       )

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004

=======================================
  Chem Name   : n-Butanol
  Molecular Wt: 74.12
  Henry's LC  : 8.81e-006 atm-m3/mole (Henry database)
  Vapor Press : 7.78 mm Hg  (Mpbpwin program)
  Log Kow     : 0.88  (Kowwin program)
  Soil Koc    : 3.11  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       0.255           30           0
   Water     99.6            208          1000
   Soil      0.0177          208          0
   Sediment  0.157           832          0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
   Air       1.91e-012    13.4        5.81        1.34        0.581
   Water     1.35e-010    754         226         75.4        22.6
   Soil      7.07e-013    0.134       0           0.0134      0
   Sediment  9.89e-011    0.298       0.00715     0.0298      0.000715
```

```
  Persistence Time: 227 hr
  Reaction Time:    296 hr
  Advection Time:   979 hr
  Percent Reacted:  76.8
  Percent Advected: 23.2

  Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
     Air:      29.95
     Water:    208.1
     Soil:     208.1
     Sediment: 832.3
       Biowin estimate: 3.494  (days-weeks)

  Advection Times (hr):
     Air:      100
     Water:    1000
     Sediment: 5e+004

=====================================
  Chem Name   : 2-Ethyl-1,3-hexanediol
  Molecular Wt: 146.23
  Henry's LC  : 1.37e-008 atm-m3/mole (Henry database)
  Vapor Press : 0.003 mm Hg  (Mpbpwin program)
  Log Kow     : 1.6  (Kowwin program)
  Soil Koc    : 16.3  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
  Air       5.57e-005       11.5         0
  Water     99.8            360          1000
  Soil      0.00397         360          0
  Sediment  0.222           1.44e+003    0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
  Air       3.19e-016    0.0114      0.00191     0.00114     0.000191
  Water     1.6e-013     658         342         65.8        34.2
  Soil      1.02e-016    0.0261      0           0.00261     0
  Sediment  1.28e-013    0.366       0.0152      0.0366      0.00152

  Persistence Time: 343 hr
  Reaction Time:    520 hr
  Advection Time:   1e+003 hr
  Percent Reacted:  65.8
  Percent Advected: 34.2

  Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
     Air:      11.55
     Water:    360
     Soil:     360
     Sediment: 1440
       Biowin estimate: 3.196  (weeks       )

  Advection Times (hr):
     Air:      100
     Water:    1000
     Sediment: 5e+004


  Chem Name   : 2-Ethylhexyl-1,3-dibutyrate
  Molecular Wt: 286.42
  Henry's LC  : 3.7e-006 atm-m3/mole (Henrywin program)
  Vapor Press : 0.00147 mm Hg  (Mpbpwin program)
  Log Kow     : 5.17  (Kowwin program)
  Soil Koc    : 6.06e+004  (calc by model)
```

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0322	14.6	0
Water	55.5	360	1000
Soil	0.0115	360	0
Sediment	44.4	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.47e-013	8.17	1.73	0.817	0.173
Water	1.75e-011	573	298	57.3	29.8
Soil	3.03e-017	0.118	0	0.0118	0
Sediment	5.28e-012	115	4.77	11.5	0.477

Persistence Time: 536 hr
Reaction Time: 770 hr
Advection Time: 1.76e+003 hr
Percent Reacted: 69.6
Percent Advected: 30.4

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 14.64
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 2.847 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Chem Name : n-butyl-n-butyrate
Molecular Wt: 144.22
Henry's LC : 0.000687 atm-m3/mole (Henry database)
Vapor Press : 1.76 mm Hg (Mpbpwin program)
Log Kow : 2.83 (Kowwin program)
Soil Koc : 277 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	4.51	24.2	0
Water	94.9	208	1000
Soil	0.0256	208	0
Sediment	0.561	832	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.3e-011	220	77	22	7.7
Water	3.86e-009	540	162	54	16.2
Soil	1.66e-012	0.146	0	0.0146	0
Sediment	1.49e-009	0.798	0.0192	0.0798	0.00192

Persistence Time: 171 hr
Reaction Time: 224 hr
Advection Time: 714 hr
Percent Reacted: 76.1
Percent Advected: 23.9

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 24.22
Water: 208.1
Soil: 208.1
Sediment: 832.3
Biowin estimate: 3.319 (days-weeks)

```
 Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004

Level III Fugacity Model (Full-Output):
=======================================
  Chem Name   : n-butyraldehyde
  Molecular Wt: 72.11
  Henry's LC  : 0.000115 atm-m3/mole (Henry database)
  Vapor Press : 108 mm Hg  (Mpbpwin program)
  Log Kow     : 0.88  (Kowwin program)
  Soil Koc    : 3.11  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       1.07            10.9         0
   Water     98.7            360          1000
   Soil      0.0105          360          0
   Sediment  0.175           1.44e+003    0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
   Air       9.87e-012    185         29.1        18.5        2.91
   Water     2.14e-009    517         269         51.7        26.9
   Soil      6.74e-012    0.055       0           0.0055      0
   Sediment  1.77e-009    0.23        0.00954     0.023       0.000954

   Persistence Time: 272 hr
   Reaction Time:    387 hr
   Advection Time:   914 hr
   Percent Reacted:  70.2
   Percent Advected: 29.8

   Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
      Air:      10.92
      Water:    360
      Soil:     360
      Sediment: 1440
        Biowin estimate: 3.062  (weeks       )

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004


Chem Name   : 2-Ethylhexanol
  Molecular Wt: 130.23
  Henry's LC  : 2.65e-005 atm-m3/mole (Henry database)
  Vapor Press : 0.185 mm Hg  (Mpbpwin program)
  Log Kow     : 2.73  (Kowwin program)
  Soil Koc    : 220  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       0.523           19.4         0
   Water     98.9            208          1000
   Soil      0.0168          208          0
   Sediment  0.519           832          0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
   Air       2.17e-012    41.2        11.5        4.12        1.15
   Water     2.22e-010    728         218         72.8        21.8
   Soil      7.5e-014     0.123       0           0.0123      0
   Sediment  9.28e-011    0.954       0.0229      0.0954      0.00229
```

```
 Persistence Time: 221 hr
 Reaction Time:    287 hr
 Advection Time:   960 hr
 Percent Reacted:  77
 Percent Advected: 23

 Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
    Air:      19.4
    Water:    208.1
    Soil:     208.1
    Sediment: 832.3
      Biowin estimate: 3.370  (days-weeks  )

 Advection Times (hr):
    Air:      100
    Water:    1000
    Sediment: 5e+004

Chem Name   : 2,4-Diethyloctane-1-ol
Molecular Wt: 186.34
Henry's LC  : 9.63e-005 atm-m3/mole (Henrywin program)
Vapor Press : 0.00273 mm Hg  (Mpbpwin program)
Log Kow     : 4.62  (Kowwin program)
Soil Koc    : 1.71e+004  (calc by model)

        Concentration   Half-Life    Emissions
          (percent)        (hr)       (kg/hr)
 Air       0.865           13.1         0
 Water     79.6            360          1000
 Soil      0.0233          360          0
 Sediment  19.6            1.44e+003    0

           Fugacity    Reaction    Advection   Reaction    Advection
            (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
 Air       3.82e-012    154         29.1        15.4        2.91
 Water     6.74e-010    516         268         51.6        26.8
 Soil      5.49e-015    0.151       0           0.0151      0
 Sediment  2.07e-010    31.7        1.32        3.17        0.132

 Persistence Time: 337 hr
 Reaction Time:    480 hr
 Advection Time:   1.13e+003 hr
 Percent Reacted:  70.2
 Percent Advected: 29.8

 Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
    Air:      13.12
    Water:    360
    Soil:     360
    Sediment: 1440
      Biowin estimate: 3.246  (weeks       )

 Advection Times (hr):
    Air:      100
    Water:    1000
    Sediment: 5e+004

Chem Name   : 2,4-Diethyloctane-1,5-diol
Molecular Wt: 202.34
Henry's LC  : 2.22e-006 atm-m3/mole (Henrywin program)
Vapor Press : 6.62e-005 mm Hg  (Mpbpwin program)
Liquid VP   : 8.59e-005 mm Hg  (super-cooled)
Melting Pt  : 36.5 deg C (Mpbpwin program)
Log Kow     : 3.49  (Kowwin program)
Soil Koc    : 1.27e+003  (calc by model)
```

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0246	8.99	0
Water	97.6	360	1000
Soil	0.0175	360	0
Sediment	2.35	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.02e-013	6.57	0.852	0.657	0.0852
Water	1.85e-011	650	338	65	33.8
Soil	1.2e-015	0.116	0	0.0116	0
Sediment	7.12e-012	3.92	0.163	0.392	0.0163

Persistence Time: 346 hr
Reaction Time: 524 hr
Advection Time: 1.02e+003 hr
Percent Reacted: 66.1
Percent Advected: 33.9

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 8.986
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.072 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Chem Name : 2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol-2)
Molecular Wt: 202.34
Henry's LC : 2.22e-006 atm-m3/mole (Henrywin program)
Vapor Press : 4.75e-005 mm Hg (Mpbpwin program)
Liquid VP : 6.26e-005 mm Hg (super-cooled)
Melting Pt : 37.1 deg C (Mpbpwin program)
Log Kow : 3.49 (Kowwin program)
Soil Koc : 1.27e+003 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.028	10.5	0
Water	97.6	360	1000
Soil	0.0213	360	0
Sediment	2.35	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.15e-013	6.42	0.97	0.642	0.097
Water	1.85e-011	650	338	65	33.8
Soil	1.46e-015	0.142	0	0.0142	0
Sediment	7.12e-012	3.92	0.163	0.392	0.0163

Persistence Time: 346 hr
Reaction Time: 524 hr
Advection Time: 1.02e+003 hr
Percent Reacted: 66.1
Percent Advected: 33.9

```
Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
   Air:      10.47
   Water:    360
   Soil:     360
   Sediment: 1440
     Biowin estimate: 3.072  (weeks       )

Advection Times (hr):
   Air:      100
   Water:    1000
   Sediment: 5e+004
```

```
Chem Name   : 2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)
Molecular Wt: 244.42
Henry's LC  : 5.2e-006 atm-m3/mole (Henrywin program)
Vapor Press : 3.62e-006 mm Hg  (Mpbpwin program)
Liquid VP   : 7.33e-006 mm Hg  (super-cooled)
Melting Pt  : 56 deg C (Mpbpwin program)
Log Kow     : 4.89  (Kowwin program)
Soil Koc    : 3.18e+004  (calc by model)
```

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0371	8.84	0
Water	69.3	360	1000
Soil	0.0652	360	0
Sediment	30.6	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.49e-013	13.1	1.68	1.31	0.168
Water	3.17e-011	602	313	60.2	31.3
Soil	4.55e-016	0.567	0	0.0567	0
Sediment	9.61e-012	66.5	2.77	6.65	0.277

```
Persistence Time: 452 hr
Reaction Time:    662 hr
Advection Time:   1.42e+003 hr
Percent Reacted:  68.3
Percent Advected: 31.7

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
   Air:      8.844
   Water:    360
   Soil:     360
   Sediment: 1440
     Biowin estimate: 2.979  (weeks)

Advection Times (hr):
   Air:      100
   Water:    1000
   Sediment: 5e+004
```

```
Chem Name   : 2-Ethylhexyl-n-butyl ether
Molecular Wt: 186.34
Henry's LC  : 0.0173 atm-m3/mole (Henrywin program)
Vapor Press : 0.262 mm Hg  (Mpbpwin program)
Log Kow     : 4.9  (Kowwin program)
Soil Koc    : 3.26e+004  (calc by model)
```

```
          Concentration   Half-Life    Emissions
            (percent)       (hr)       (kg/hr)
Air         1.73            7.32         0
Water       77.4            208          1000
Soil        0.00918         208          0
Sediment    20.9            832          0

            Fugacity    Reaction    Advection   Reaction    Advection
             (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
Air         4.25e-012    307         32.4        30.7        3.24
Water       6.39e-008    483         145         48.3        14.5
Soil        1.13e-013    0.0573      0           0.00573     0
Sediment    1.16e-008    32.6        0.783       3.26        0.0783

Persistence Time: 187 hr
Reaction Time:    228 hr
Advection Time:   1.05e+003 hr
Percent Reacted:  82.2
Percent Advected: 17.8

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
   Air:      7.318
   Water:    208.1
   Soil:     208.1
   Sediment: 832.3
     Biowin estimate: 3.375  (days-weeks)

Advection Times (hr):
   Air:      100
   Water:    1000
   Sediment: 5e+004
```

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Conclusion : The components of EP-204 distribute primarily to water. The more volatile components have some distribution to air and 2-ethylhexyl-1,3-dibutyrate, 2,4-Diethyloctane-1-ol and 2,4,6-Triethyl-3-propylheptane-1,7-diol (the C16-diol) have significant distributions in sediment. Soil distribution is not considered important for any component under these conditions of 100% release to water.

COMPONENT	AIR	WATER	SOIL	SEDIMENT
2-Ethylhexanol	0.52	98.9	0.02	0.52
2-Ethylhexenal	0.94	98.4	0.01	0.61
2-Ethylhexanal	1.81	97.5	0.01	0.67
n-Butanol	2.55	99.6	0.02	0.16
2-Ethyl-1,3-hexanediol	<0.1	99.8	0.01	0.22
2-Ethylhexyl-1,3-dibutyrate	0.03	55.5	0.01	44.4
n-Butyl-n-butyrate	4.51	94.9	0.03	0.56
n-Butyraldehyde	1.07	98.7	0.01	0.18
2,4-Diethyloctane-1-ol	0.87	79.6	0.02	19.6
2,4-Diethyloctane-1,5-diol	0.02	97.6	0.02	2.35
2-Ethyl-3-propyl-4-hydroxy methylhexane-1-ol (C12-diol-2)	0.03	98.9	0.02	1.06
2,4,6-Triethyl-3-propyl heptane-1,7-diol (C16-diol)	0.04	69.3	0.06	30.6
2-Ethylhexyl-n-butyl ether	1.74	77.4	0.01	20.9

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method are assigned a reliability of 2

Flag : Critical study for SIDS endpoint

10.02.2004 (10)

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other: Laboratory treatment plant using domestic and synthetic-chemical wastes
Concentration	:	28 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	= 60 - 70 (±) % after 28 day(s)
Result	:	
Kinetic of testsubst.	:	5 day(s) = 15 % 10 day(s) = 29 % 17 day(s) = 44 % 24 day(s) = 58 % 28 day(s) = 70 %
Control substance	:	Aniline
Kinetic	:	10 day(s) = 66 % 28 day(s) = 75 %
Method	:	Carbon dioxide evolution test. OECD 301 B (1993) guideline also in accord with ISO 9493:1990
Result	:	See kinetics
Test substance	:	CASNO 68609-68-7 tested as Oxooel 800
Conclusion	:	The test material is biodegradable but does not fully meet the OECD criteria for "readily biodegradable".
Reliability	:	(1) valid without restriction OECD 301 B guideline test under GLP with no deviations.
Flag	:	Critical study for SIDS endpoint

24.12.2004 (5)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : other: calculated from components
Species :
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 9.5 calculated

Method :

An estimate of the toxicity of aquatic toxicity of EP-204 was made by using the principle of additivity. If the components are lumped together, assuming no specific joint-toxic action and the same mechanism of action, a rough estimate of the toxicity of EP-204 can be calculated. This is done by summing the individual component's fraction divided by its EC50, dividing this summation by the sum of the fractions (to normalize to 100%) and taking the reciprocal. The EC50 values used are the experimental or estimated single values and the geometric mean if a range of EC50 values found in the literature or estimated from ECOSAR using the seutral organics model

Remark :

Source of LC50 values for fish

2,4-Diethyloctane-1,5-diol: ECOSAR estimate

2-Ethyl-1,3-hexanediol: ECOSAR estimate

2-Ethylhexanol: Value from IUCLID 2000 document for 2-Ethylhexanol (CASNO 104-76-7).

2-Ethylhexenal: Huels AG: Report No. FK 1368, 1997 (unpublished) as cited in IUCLID 2000 document for
2-Ethylhexenal (CASNO 645-62-5).

2-Ethylhexanal: Hoechst AG, unveroeffentlichte Untersuchung 79.0533, (1979) zitiert im Hoechst-GDS vom 29.04.1994 as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).

n-Butanol: Value from IUCLID 2000 document for n-Butanol (CASNO 71-36-3).

Result :

The calculation for the estimated LC50 for fish is:

Calculation of Estimated LC50 for Fish

Component	[%]	LC50	1/LC50	x[%]
2,4-Diethyloctane-1,5-diol	22.5	6.0	0.166667	3.75
2-Ethyl-1,3-hexanediol	10	257	0.003891	0.038911
2-Ethylhexanol	10	24.4	0.040984	0.409836
2-Ethylhexenal	5	6	0.166667	0.833333
2-Ethylhexanal	5	8	0.125	0.625
n-Butanol	1	1000	0.001	0.001
%Total	[53.5]	Sum of column		5.65808

Sum divided by total [%] 0.105759
1/x = Estimated LC50 9.5 mg/L

Test substance	:	Various individal componets of EP-204, CASNO 68609-68-7
Reliability	:	(2) valid with restrictions Estimations conducted by an acceptable method are assigned a reliability of 2
Flag	:	Critical study for SIDS endpoint

07.11.2004 (11)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	= 12.5 measured/nominal
EC50	:	= 52 calculated
EC100	:	= 100 measured/nominal
Analytical monitoring	:	yes
Method	:	other: Directive 79/831/EEC, Annex V, Part C, Update of Nov 1989
Year	:	1989
GLP	:	yes
Test substance	:	other TS

Method :

A static toxicity test was conducted using covered 50-ml beakers containing about 20 ml test solution. The dilution water was M4 medium prepared from ultrapure water. The test substance was dissolved in media at a nominal concentration of 100 mg/L by stirring for about 20 hours at 22°. Undissolved test substance was removed by centrifugation for 20 minutes at approximately 17700 G. This stock solution was diluted with test medium to make the final concentrations shown in the table. Groups of 20 daphnids in four replicates of 5 animals were exposed for 48 hours to 6 concentrations of test material and control media. Animals were examined at 0, 3, 6, 24 and 48 hours for signs of toxic effects. Oxygen concentration and pH were measured at 0 and 48 hours using additional replicates. Analytical measurements of test substance concentration was conducted at 0 and 48 hours by extraction of the test media with solvent and capillary GC analysis.

Statistical methods:
The EC50 was assessed using a graphical method on log-probit paper according to Finney Probit Analysis 1971

Result :

Visual inspection of the beakers indicated that some insoluble oily material existed in the test-concentration range.

Concentrations tested and corresponding percent immobilization of Daphnia magna.

CONC mg/L	PERCENT IMMOBILIZATION 24-Hrs	48-Hrs
Control	0	0
3.13	0	0
6.25	0	0
12.5	0	0
25	35	35
50	35	40
100	90	100

Analytical results (concentrations of 3.13, 12.5 and 100 mg/L were measured) showed that the measured concentrations varied from 95.9 - 98.0% of nominal at the start of the study and 95.9 to 105% of nominal at the end (48 hours). From the description of the method, the analysis was conducted by an extraction of the total amount of test medium including any non-dissolved oil that may have been in the test vessel.

Test condition :

Animals were less than 24 hours old at the start of the test and were not fed during the test. During the 48-hour toxicity test, the pH and dissolved oxygen ranged from 7.9 to 8.0 and 7.0 to 8.4 mg/L, respectively. The test temperature was 18-22 °C, the alkalinity was 0.8 to 1.0 mmol/L and hardness 2.2 to 3.1 mmol/L.

Test substance :

CASNO 68609-68-7 tested as Oxo oil 800 (in english report).

Analysis of the test material, based on gc peak areas, was reported as:

2,4-Diethyl-1,5-octanediol	51.9%
2-Ethyl-1,3-hexanediol	9.1%
2-Ethylhexanol	12.6%
Diethyloctanol	5 - 10%
High-boiling components	20%

Conclusion :

Under these conditions, the 48-hour EC50 for Daphnia magna is 52 mg/L and the EC0 is 12.5 mg/L

Reliability : (1) valid without restriction

Guideline study under GLPs with ananlysis of test material and test solutions.

Flag : Critical study for SIDS endpoint

11.02.2004 (8)

Type : other: Calculated from individual components
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 12.9 calculated

Method :

An estimate of the toxicity of aquatic toxicity of EP-204 was made by using the principle of additivity. If the components are lumped together, assuming no specific joint-toxic action and the same mechanism of action, a rough estimate of the toxicity of EP-204 can be calculated. This is done by

summing the individual component's fraction divided by its EC50, dividing this summation by the sum of the fractions (to normalize to 100%) and taking the reciprocal. The EC50 values used are the experimental or estimated single values and the geometric mean if a range of EC50 values found in the literature or estimated from ECOSAR using the seutral organics model

Remark :

Source of EC50 values for daphnia

2,4-Diethyloctane-1,5-diol: ECOSAR estimate

2-Ethyl-1,3-hexanediol: ECOSAR estimate

2-Ethylhexanol: Value from IUCLID 2000 document for 2-Ethylhexanol (CASNO 104-76-7).

2-Ethylhexenal: BASF AG, Oekologie-Labor; unveroeffentl. Untersuchung (1165/87) as cited in IUCLID 2000 document for 2-Ethylhexenal (CASNO 645-62-5).

2-Ethylhexanal: BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung, (0423/88) as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).

n-Butanol: Value from IUCLID 2000 document for n-Butanol (CASNO 71-36-3).

Result :

Calculation of Estimated EC50 for Daphnia

Component	[%]	EC50	1/EC50	x[%]
2,4-Diethyloctane-1,5-diol	22.5	7.1	0.140845	3.169014
2-Ethyl-1,3-hexanediol	10	268	0.003731	0.037313
2-Ethylhexanol	10	39	0.025641	0.25641
2-Ethylhexenal	5	20	0.05	0.25
2-Ethylhexanal	5	11.5	0.086957	0.434783
n-Butanol	1	1000	0.001	0.001
%Total	[53.5]		Sum of column	4.14852

Sum divided by total [%]	0.077542
1/x = Estimated LC50	12.9 mg/L

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method are assigned a reliability of 2

07.11.2004 (11)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae
Endpoint : other: calculated EC50
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 19.3 calculated

Method :

An estimate of the toxicity of aquatic toxicity of EP-204 was made by using the principle of additivity. If the components are lumped together, assuming no specific joint-toxic action and the same mechanism of action, a rough estimate of the toxicity of EP-204 can be calculated. This is done by summing the individual component's fraction divided by its EC50, dividing this summation by the sum of the fractions (to normalize to 100%) and taking the reciprocal. The EC50 values used are the experimental or estimated single values and the geometric mean if a range of EC50 values found in the literature or estimated from ECOSAR using the seutral organics model

Remark :

Source of EC50 values for alga

2,4-Diethyloctane-1,5-diol: ECOSAR estimate

2-Ethyl-1,3-hexanediol: ECOSAR estimate

2-Ethylhexanol: Value from IUCLID 2000 document for 2-Ethylhexanol (CASNO 104-76-7).

2-Ethylhexenal: BASF AG(1988), Labor Oekologie: Unveroeffentlichte Untersuchung: Algentest vom 16.06.1988 (2/x165/87/t72) as cited in IUCLID 2000 document for 2-Ethylhexenal (CASNO 645-62-5).

2-Ethylhexanal: BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung, (0423/88) as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).

n-Butanol: Value from IUCLID 2000 document for n-Butanol (CASNO 71-36-3).

Result :

Calculation of Estimated EC50 for Green Alga

Component	[%]	EC50	1/EC50	x[%]
2,4-Diethyloctane-1,5-diol	22.5	4.8	0.208333	4.6875
2-Ethyl-1,3-hexanediol	10	164	0.006098	0.060976
2-Ethylhexanol	10	16	0.0625	0.625
2-Ethylhexenal	5	19.3	0.051813	0.259067
2-Ethylhexanal	5	52	0.019231	0.096154
n-Butanol	1	100	0.01	0.01
%Total	[53.5]		Sum of column	5.738697

Sum divided by total [%]	0.107265
1/x = Estimated LC50	19.3 mg/L

Test substance :

Various individal componets of EP-204, CASNO 68609-68-7

Reliability : (2) valid with restrictions

Estimations conducted by an acceptable method are assigned a reliability of 2

Flag : Critical study for SIDS endpoint

07.11.2004 (11)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	CMC
Doses	:	5000 mg/kg
Method	:	
Year	:	
GLP	:	yes
Test substance	:	

Method :

Groups of five Wistar rates of each sex were dosed by gavage with test material suspended in CMC. Rats had been fasted overnight prior to dosing. Rats were maintained on 12 hour light:dark cycle at 20-24 deg C and 30-70% relative humidity. Rats were observed for 14 days after dosing, sacrificed and macroscopically examined for signs of adverse effects. Animals were weighed as groups on days 3, 7 and 10 of study.

Result :

Mortality;
males 0/5
females 2/5 (day 1 and day 2)

Group bodyweight gain was normal.

Clinical sings included difficulty breathing, loss of equilibrium, piloerection, atony, and general poor condition persisting about 24 hours. Salivation was reported the first 2 to 4 hours after administration.

No chemically related findings were reported at necropsy

Test substance :

CASNO 68609-68-7 tested as Oxoel 800

Conclusion :

The oral LD50 of the test substance is > 5000 mg/kg-bw in male and female Wistar rats.

Reliability : (1) valid without restriction

Guideline like study conducted under GLP

Flag : Critical study for SIDS endpoint

07.11.2004 (14)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: Inhalation risk test
Value	:	> .11 mg/l
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	

Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	Six Wistar rats of each sex were exposed to a saturated vapor of the test material generated at 20° C for a period of 7 hours.
Result	:	The nominal concentration calculated from the flow rate and material loss was 0.11 mg/L. No animals died during exposure or in the 14-day observation period. No significant clinical signs were observed.
Test substance	:	CASNO 68609-68-7 tested as Oxoel 800
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

07.11.2004 (19)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	5 days/week
Post exposure period	:	none
Doses	:	0, 25, 125, 250 or 500 mg/kg-bw
Control group	:	yes, concurrent vehicle
NOAEL	:	= 125 mg/kg bw
LOAEL	:	= 250 mg/kg bw
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS
Method	:	Animals. F344 rats, 36- to 37-days-old at delivery, were kept singly in stainless steel wire cages. Mean body weight ranges at dosing were (male) 105-114 g and (female) 86-97 g. Animals were acclimated 6 days on a 12-hr photoperiod at 20-24°C and 30-70% relative humidity; food and water were ad lib. In the 13-week study groups of 10 animals of each sex rats received daily oral gavage doses of 0, 25, 125, 250 or 500 mg/kg on 5 consecutive days per week. Doses were prepared daily by dispersing TS in an aqueous solution of Cremophor EL (5 mg/100 ml). Dosing volume was 10 ml/kg, based on weekly body weights. Controls received 5.0 ml/kg vehicle. Concentrations and homogeneity were checked by gas chromatographic

analysis of samples from each dose level at study start and periodically during the 13-week study. Animals were fasted for about16 hr after the last dose and terminated by decapitation under CO2 anesthesia.

In-life observations. Animals were inspected twice daily for morbidity and mortality but only once daily on nontreatment days. Clinical observations were made daily. Body weights were determined on day 01 and weekly thereafter. Animals were palpated on weighing. Average daily food consumption was determined weekly. Blood was collected by retroorbital bleeding from fasted animals on the morning of Days 29 and 84. Standard serum enzyme activities and biochemistry measurements were recorded. Hematology parameters were leucocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, differential leucocytes, and reticulocytes.

Observations at necropsy. Moribund animals were euthanized and dead and euthanized animals were immediately necropsied for gross pathology. At scheduled terminations body and organ weights were measured. At study termination adrenals, brains, kidneys, livers, stomachs, testes, and ovaries from all animals were weighed, and with other organs and tissues listed in U.S. EPA Health Effects Guidelines (1987b) fixed in 4% formalin. All tissues from high dose and control animals were stained with hematoxylin-eosin and examined microscopically. Lungs, livers, spleens, kidneys, stomachs, sternums, femurs, and femur bone marrows were examined microscopically at intermediate dose levels. Skin, eyes, female mammary glands, thigh musculatures, and extraorbital lacrymatory glands were not examined in the absence of signs of toxicity. Livers were also stained with oil red for reticulolipid content and examined microscopically.

Ancillary studies were used only to determine hepatic peroxisome proliferation. Livers were removed at termination and weighed, and cyanide-insensitive pCoA activities and protein concentrations were determined.

Statistical treatment of data. Means and standard deviations were calculated for body weights, food and water consumption, clinical pathology results, and organ weights. Values for test groups were compared with controls in the main study by ANOVA followed by Dunnett's test.

Result :

No rat died on test. There was deacreased weight gain in male and female rats at 500 mg/kg, starting at Week 4 in males and Week 11 in females, amounting to weight losses of 7% in males and 6% in females by Week 13. There were no differences from controls at any treatment level in food consumption.

Clinical pathology. Differences from control values were seen mostly at 84 days. Females at 250 and 500 mg/kg had 30 and 36% decreases in serum ALT activities, respectively. Females at 500 mg/kg had a 16% decrease in serum cholesterol concentration and males at 500 mg/kg had 13% decreases in total protein and albuminconcentrations. There was a 25% increase in reticulocyte numbers in male and female rats at 500 mg/kg.

Necropsy findings: Relative organ weights. Significant differences from controls in rats were moderate and limited to the brain, kidneys, liver, stomach, and testes at 250 and 500 mg/kg (Table 3). Male rat relative brain weights increased by 6% at 500 mg/kg, male kidney weights by 8% at 250

and 16% at 500 mg/kg, male liver weights by 8% at 250 and 29% at 500 mg/kg, male stomach weights by 11% at 500 mg/kg, and testis weights by 5.5% at 500 mg/kg. Female's kidney weights increased by 5% at 250 and 6% at 500 mg/kg, female liver weights by 8% at 250 and 15% at 500 mg/kg, and female stomach weights by 6% at 250 and 16% at 500 mg/kg.

Necropsy findings: Gross observations. Gross lesions differing from controls 500 mg/kg only. 2/10 males and 4/10 females exhibited single or multiple slightly elevated foci in the forestomach. There were no other gross findings.

Necropsy findings: Microscopic findings. Dose-related findings were limited to the forestomach and liver at 500 mg/kg. There was a generalized acannothosis of the forestomach mucosa in 1/10 males with ballooning degeneration of the epithelial wall and acanthosis of the forestomach mucosa in 2/10 males and 5/10 females.There was a moderate decrease in hepatic peripheral lobular fatty infiltration in 4/10 males and 2/10 females and adrenal b-cell hyperplasia in 3/10 females.

Peroxisome proliferation. Hepatic peroxisome proliferation was determined in ancillary 13-week studies by measuring activity of hepatic cyanide-insensitive palmitoyl Coenzyme A in livers at termination. Increases in pCoA activity were 6.5-fold in male rats and 3.4-fold in females at 500 mg/kg, with decreases in body weight gain similar to those in the main study.

Relative Organ Weights at Termination (grams (SD))Weights at other dose levels (25 and 125 mg/kg) did not differ from controls

Males	0	250	500
Brain	0.68 (0.03)	0.70 (0.02)	0.72 (0.02)**
Kidneys	0.69 (0.02)	0.75 (0.02)**	0.81 (0.04)**
Liver	2.77 (0.11)	2.98 (0.08)**	3.57 (0.22)**
Stomach	0.57 (0.03)	0.58 (0.03)	0.63 (0.02)**
Testes	1.11 (0.05)	1.16 (0.07)	1.17 (0.06)*

Females	0	250	500
Brain	1.07 (0.03)	1.1 (0.06)	1.1 (0.04)
Kidneys	0.77 (0.02)	0.81 (0.03)*	0.82 (0.03)**
Liver	2.67 (0.11)	2.88 (0.08)**	3.07 (0.07)**
Stomach	0.71 (0.03)	0.75 (0.03)*	0.82 (0.04)**
Ovaries	0.041(0.003)	0.037(0.005)*	0.039(0.004)

*p 0.05
** p 0.01

Test substance :

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)Purity 99.8% purity by gas chromatography

Conclusion :

The 500-mg/kg dose was associated with significant peroxisome proliferation and systemic toxicity as evidenced by small but statistically significant ($p < 0.01$) reduction in weight gain in rats of each sex. Target organs were the liver and forestomach. The possible testes effects were of special interest and there was a slight increase in relative testis weight at 500 mg/kg but this was not correlated with any morphological changes.

The reduced relative ovarian weight at 250 mg/kg did not occur at 500 mg/kg and is considered incidental. It is concluded that 125 mg/kg was a NOEL based on organ weight changes at 250 mg/kg.

Reliability : (2) valid with restrictions

Published studies are assigned a 2

Flag : Critical study for SIDS endpoint

10.11.2004 (4)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse mutation assay
System of testing : Salmonella
Test concentration : Varies
Cycotoxic concentr. : See Results
Metabolic activation : with and without
Result : negative
Method : other: National Toxicology Program
Year :
GLP : no data
Test substance : other TS

Method :

As each stain of Salmonella typhimurium is genetically different, using several strains in a test increases the opportunity of detecting a mutagenic chemical. All strains of Salmonella typhimurium used for mutagenicity testing carry a defective (mutant) gene that prevents them from synthesizing the essential amino acid histidine. Mutations leading to the ability to sysntesize histidine are called "back" or "reverse" mutations and the process is referred to as "reversion."

Some test protocols utilize extracts of Aroclor rat or hamster liver enzymes (S9) to promote metabolic conversion of the test chemical. This is necessary since the Salmonella bacterium does not have the mamillian metabolic capabilities.

In the Salmonella assay, a test tube containing a suspension of one strain of Salmonella typhimurium plus S9 mix or plain buffer without S9, is incubated for 20 minutes at 37º C with the test chemical. Control cultures, with all the same ingredients except the test chemical, are also identically incubated. In addition, positive controls with a known potent mutagen, are prepared. After 20 minutes, agar is added to the cultures and the contents of the tubes are thoroughly mixed and poured onto the surface of petri dishes containing standard bacterial culture medium. The plates are incubated, and bacterial colonies that do not require an excess of supplemental histidine appear and grow. These colonies are comprised of Salmonella that have undergone reverse mutation to restore function of the histidine-manufacturing gene. The number of colonies is counted after 2 days.

Several doses (at least 5) of each test chemical and multiple strains of Salmonella typhimurium are used in each experiment. In addition, cultures are set up with and without added S9 liver enzymes at 10% concentration in these studies. ***The pattern and the strength of the mutant response are taken into account in determining the mutagenicity of a chemical. All observed responses are verified in repeat tests. If no increase in mutant

colonies is seen after testing several strains under several different culture conditions, the test chemical is considered to be nonmutagenic in the Salmonella test.

ReferenceMortelmans K, Zeiger E. The Ames Salmonella/microsome mutagenicity assay. Mutat Res. 2000 Nov 20;455(1-2):29-60.

Result :

Summary Information
Study Vehicle: DMSO
Protocol: Preincubation
Result: Negative

Strain: TA100

Dose	No Act (Neg)		No Act (Neg)		10% RLI (Neg)		10% RLI (Neg)		10% HLI (Neg)		10% HLI (Neg)	
ug/Pt.	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
VC	130	0.3	133	2.9	101	10.7	100	4	124	7.8	124	8.2
3.3	123	1.9	118	9.6	116	39.1	122	3.8	116	16.3	127	42.2
10	137	4.6	111	7.5	119	1	109	10.4	111	9.9	129	43.6
33	134	4.9	115	12.5	115	5.9	116	10.7	117	8.4	99	3.5
100	115	4.5	137	1.8	107	7.2	96	1.7	110	12.4	112	8.8
220			109s	4.9			114	14.5			126	5.4
333	21	0			158	0			180	0		
PC	1133	52	1284	34	800	36	1379	56	973	95.7	1459	98.6

Strain: TA1535

Dose	No Act (Neg)		No Act (Neg)		10% RLI (Neg)		10% RLI (Neg)		10% HLI (Neg)		10% HLI (Neg)	
ug/Pt.	Mn	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
VC	27	3	33	2.3	11	0.7	17	3.8	15	3.2	13	2.7
3.3	27	3.8	33	1	14	1.8	17	1	14	2.1	17	2.6
10	27	3	27	2.7	15	1.8	14	0.3	16	4.1	14	2.6
33	27	1.2	35	0.3	15	1.2	14	1.7	12	3.8	18	0.6
100	22	4.3	31	2.2	12	1.8	13	1.3	13	0.6	14	1
220			25s	2.6			14	0.6			14	2.9
333	T	0			8	0			5s	1.8		
PC	835	13	902	21	66	3.8	91	10.2	84	3.9	90	2.6

Strain: TA1537

Dose	No Act (Neg)		No Act (Neg)		No Act (Neg)		10% RLI (Neg)		10% RLI (Neg)		10% HLI (Neg)		10% HLI (Neg)	
ug/Pt.	Mean	sem	Mean	sem	Mea	sem	Mn	sem	Mn	sem	Mn	sem	Mean	sem
VC	6	0.7	6	0.3	5	0.7	6	1.2	6	0.9	6	1	9	2.6
3.3	8	1.2	4	0.6	6	1.5	5	0.3	7	2.1	5	1.2	9	1.7
10	11	1.9	5	1.2	8	1.9	7	2.5	8	1.5	6	1.5	8	2.2
33	11	2.3	6	0.9	5	0.6	7	1	4	0.7	6	1.2	7	1.5
100	13	2.3	5	1.5	7	2	5	0.7	8	1.8	6	1.2	9	0.9
220					6s	1.7			9	1.2			8	2.6
333	173	0	339	0			12s	2			188s	1		
PC	133	10.7	468	69	370	59	73	4.3	98	11.7	82	7.7	117	38.9

Strain: TA98

Dose	No Act (Neg)		No Act (Neg)		10% RLI (Neg)		10% RLI (Neg)		10% HLI (Neg)		10% HLI (Neg)	
ug/Pt.	Mean	sem	Mn	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
VC	17	1.3	18	1.5	20	1.2	20	2.6	28	4.9	33	4.9
3.3	18	1.3	17	2.6	20	3.2	22	1.5	30	0.9	24	4.7
10	12	1.2	15	2.3	23	0.7	23	1.5	24	2	29	0.3
33	16	2	22	1.2	24	4.2	24	3.2	20	2	28	3.2
100	19	1.5	19	0.6	22	2.9	25	1.3	26	1.7	26	1.7
220			18s	1			27	2.1			29	2.6
333	210	0			305	0			9s	3.8		
PC	1049	31	1289	46	544	17	855	31	960	59	820	37.5

Abbreviations:
PC = positive control
VC = vehicle control
RLI = induced male Sprague Dawley rat liver S9
HLI = induced male Syrian hamster liver S9
s = Slight Toxicity; p = Precipitate; x = Slight Toxicity and Precipitate;
T = Toxic; c = Contamination

Test substance :

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)

Conclusion :

Material was non-mutagenic in the presence or absence of standard liver metabolic activating systems

Reliability : (1) valid without restriction

NTP Guideline study with data available for review.

Flag : Critical study for SIDS endpoint

23.12.2004 (7)

Type : Chromosomal aberration test
System of testing : Chinese hamster ovary cells (CHO-W-B1)
Test concentration : See results
Cycotoxic concentr. : See results
Metabolic activation : with and without
Result : negative
Method : other: NTP Protocol
Year :
GLP : no data
Test substance : other TS

Method :

An in vitro assay for chromosomal damage was conducted in cloned Chinese hamster ovary cells (CHO-W-B1) to identify chemicals capable of inducing chromosomal aberrations (CA). The procedure is described in detail by Galloway et al. (1985, 1987). This assay only detects structural chromosomal damage; it does not detect aneuploidy.

Test chemicals were supplied to the testing laboratory as coded aliquots. The substance was tested in cultured CHO cells for induction of SCE and CA, both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 enzymes and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three concentrations of test substance; the high dose was limited by toxicity or solubility, or in the absence of either of these

factors, the high dose was limited to 5 mg/mL . A single culture flask per concentration was used. Tests yielding equivocal or positive results generally were repeated.

Cells were harvested in their first mitotic division after the initiation of chemical exposure. Without S9, cells were incubated for 8-12 hours with the test chemical in McCoy's 5A medium supplemented with fetal calf serum, L-glutamine, and antibiotics, then Colcemid was added and incubation was continued for 2 hours. The incubation time and the dose levels selected were determined from the information on cell cycling and toxicity obtained from the prior SCE test; if cell cycle delay was anticipated, the incubation period was extended to permit accumulation of sufficient cells in first metaphase for statistical analysis. The cells were harvested by mitotic shake-off, fixed, and stained with Giemsa. For the CA test with S9, cells were treated with the test chemical and S9 for 2 hrs, after which the treatment medium was removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hrs. Cells were harvested in the same way as for the treatment without S9.

Cells were selected for scoring on the basis of adequate morphology and completeness of karyotype (21 +/- 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One hundred or two hundred first-division metaphase cells were scored at each dose level. The classes of aberrations that were recorded included "simple" (breaks and terminal deletions), "complex" (rearrangements and translocations), and "other" (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Data are presented as the percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted to assess the presence of a dose-response (trend test) and the significance of the individual dose points compared to the vehicle control (Galloway et al., 1987). For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) was considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A strong trend ($P < 0.003$) with a single significant dose level was designated weak positive *, to indicate a high level of induced aberrations. A strongly positive trend ($P < 0.003$), in the absence of a statistically-significant increase at any one dose point, led to an equivocal call. Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers. Trials that gave a weak positive or positive result were repeated. The overall result for the CA assay was based on an evaluation of the responses in all trials within an activation condition.

Galloway SM, Armstrong MJ, Reuben C. et al. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Mol. Mutagen. 10(Supplement 10): 1 - 175.

Galloway SM, Bloom AD, Resnick M et al. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7: 1-51.

Result :

Activation	Trial	Trial Call
No Activation	1	Negative
Induced Rat Liver S9	2	Negative

	Dose µg/mL	Cells	Total Abs. #	Total Abs. Per Cell	Total Abs. % With Abs.	Complex Abs. #	Complex Abs. Per Cell	Complex Abs. % With Abs.	Simple Abs. #	Simple Abs. Per Cell	Simple Abs. % With Abs.	Other Abs. Ab #	Other Abs. % With Abs.
Neg	0	100	0	0	0	0	0	0	0	0	0	0	0
DMSO	0	200	1	0.005	0.5	0	0	0	1	0.01	0.5	0	0
TS	50	200	3	0.015	1	1	0.01	0.5	2	0.01	1	0	0
TS	108	200	1	0.005	0.5	1	0.01	0.5	0	0	0	0	0
TS	233	200	2	0.01	1	0	0	0	2	0.01	1	0	0
TS	500	0	0	0	0	0	0	0	0	0	0	0	0
Mito	0.1	200	40	0.2	16	21	0.11	9	19	0.1	9.5	0	0
	0.4	50	18	0.36	26	11	0.22	18	7	0.14	14	0	0
Trend:			0.366			-0.001			0.2				
Probability:			0.357			0.5			0.421				

	Dose µg/mL	Cells	Total Abs. #	Total Abs. Per Cell	Total Abs. % With Abs.	Complex Abs. #	Complex Abs. Per Cell	Complex Abs. % With Abs.	Simple Abs. #	Simple Abs. Per Cell	Simple Abs. % With Abs.	Other Abs. Ab #	Other Abs. % With Abs.
Neg	0	100	0	0	0	0	0	0	0	0	0	0	0
DMSO	0	200	1	0.005	0.5	0	0	0	1	0.01	0.5	0	0
TS	50	200	0	0	0	0	0	0	0	0	0	0	0
TS	108	200	0	0	0	0	0	0	0	0	0	0	0
TS	233	200	5	0.025	1.5	1	0.01	0.5	4	0.02	1.5	0	0
TS	500	0	0	0	0	0	0	0	0	0	0	0	0
Cyclo	5	200	32	0.16	11.5	12	0.06	5	20	0.1	7.5	0	0
	15	50	11	0.22	20	6	0.12	10	5	0.1	10	0	0
Trend:			1.346			1.343			1.346				
Probability:			0.089			0.09			0.089				

Test substance :

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)Purity 99.8% purity by gas chromatography

Conclusion :

Material did not induce chromosome aberrations in presence or absence of a metabolic activation system

Reliability : (1) valid without restriction

NTP Guideline study with data available for review.

Flag : Critical study for SIDS endpoint

23.12.2004 (7)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	mouse
Sex	:	female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	gd 1 to 17
Frequency of treatm.	:	cont
Duration of test	:	
Doses	:	90, 300 or 900 ppm
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS

Method :

Groups of 28 pregnant Swiss (CD-1) mice were treated with 2-ethylhexanol (2EH) in feed at 0, 90, 300 or 900 ppm in feed (corresponding to 0, 0.13, 0.46, 1.49 mmol/kg-day)in a microencapsulated form to prevent reaction with feed and loss of bioavailability. Dosed feed was provided as lib from gestational day 0 to gestational day 17, at which time dams were sacrificed and the products of conception were evaluated. At sacrifice, the number of ovarian corpora lutea and uterine implantation sites, including resorptions, and dead or live fetuses, were recorded. Live and dead fetuses were weighed. Live fetuses were sexed and examined for external, visceral and skeletal malformations and variations using the standard protocols employed by the NTP for developmental toxicity evaluations in mice.

Remark :

Support for a lack of developmental toxicity of 2-ethylhexanol comes from the di-2-ethylhexyl adipate fertility and developmental toxicity study in which a dose of 1080 mg/kg-day to Wistar rats was associated with minimal fetotoxicity and maternal toxicity. [ICI. 1988b. ICI Central Toxicology Laboratory. Di-(2-ethylhexyl)adipate (DEHA): Fertility study in rats. Report CTL/P/2229 (unpublished study). As cited in IRIS, US EPA.]

There is also a dermal developmental toxicity in which groups of 25 pregnant female Fischer 344 rats were treated cutaneously with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg/day for 6 hours per day on gestation days 6 through 15. No treatment-related maternal deaths or early pregnancy loss were seen in the treatment groups, but maternal weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals. Exfoliation and crusting were seen at treatment sites at all dose levels and erythema at dose levels 1.0 and 3.0 ml/kg-day. Low-dose groups, showed an increase in postimplantation loss, decreased litter size, and reduced fetal body weights but this was not observed in the high-dose group. There were no significant increases in incidence of malformations in the 2-ethylhexanol group relative to the sham treatment group. It is concluded that 2-ethylhexanol has no developmental toxicity activity by the dermal route in rats. [Developmental toxicity evaluation of 2-ethylhexanol administered cutaneously to Fischer 344 rats (final report) with attachments and cover letters dated 032189 and 050389, Bushy Run Research Center, EPA/OTS; Doc #86-890000216}

Result :

In the groups treated with 2-ethylhexanol no dams died, delivered early or were removed from study. The pregnancy rate was high (93-96%) and

similar in all groups. In the control group, one litter was fully resorbed. All other pregnant animals had live litters at the gd-17 necropsy. The numbers of live litters evaluated were 27 at 90 and 300 ppm and 26 at 0 and 900 ppm levels. No maternal toxicity observed in this study as a result of 2-ethylhexanol administration. Maternal body weights, absolute weight gains, corrected weight gains, gravid uterine weight absolute liver weight and relative liver weight were similar in all groups. Food consumption was significantly increased on gestational-day 3 in the 900 ppm group but unaffected for all other time points evaluated. The calculated consumption of 2-EH, based on gestational food consumption was 0 (0 mmol/kg), 17 (0.13 mmol/kg), 59 (0.46 mmol/kg) and 191 mg/kg/day (1.49 mmol/kg), for the 0, 90, 300 and 900 ppm groups, respectively.

Exposure to dietary 2-ethylhexanol was not associated with effects on any gestational parameters. The number of corpora lutea, uterine implantation sites (live, dead, resorbed), pre- and postimplantation loss, sex ratio (%, males) and live fetal body weight per litter (all fetuses or separately by sex) were similar across all groups. No treatment-related changes in the incidence of individual, external, visceral, skeletal or total malformations or variations were observed.

In conclusion, there were no maternal or developmental toxic effects of 2-ethylhexanol dietary exposure throughout gestation at any concentration tested with doses ranging as high as 191 mg/kg/day (1.49 mmol/kg).

Test substance :

2-Ethylhexanol CASNO 104-76-7 (component of EP-204)

Reliability : (1) valid without restriction

NTP Guideline study with data available for review.

Flag : Critical study for SIDS endpoint

23.12.2004 (9) (17)

Species	:	rat
Sex	:	female
Strain	:	Crj: CD(SD)
Route of admin.	:	dermal
Exposure period	:	gd 6 to 16, 6 hr per day
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	1.0, 2.0 or 4.0 mL/kg-day
Control group	:	yes
NOAEL maternal tox.	:	< 1 ml/kg bw
NOAEL teratogen.	:	= 1 ml/kg bw
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS

Method :

Groups of 25 timed-pregnant female CD rats received cutaneous applications of undiluted EHD at dosages of 1.0, 2.0 and 4.0 mL/kg/day for 6 hr/day under occlusion on gestational days 6-15 inclusive. A similar-sized control group received 4.0 mL/kg/day of deionized water with the same exposure regimen.

Result :

Maternal toxicity was present at 4.0 mL/kg-day (reduced body weight gains and mild skin irritation that were not statistically significant, and increased

liver weight that was statistically significant), and also minimally at 1.0 and 2.0 mL/kg-day (mild skin irritation and slightly increased but statistically significant relative liver weight to body weight ratio). At 4.0 mL/kg-day there was one visceral malformation (unilateral hydroureter), increased incidences of three visceral variants (atelectasis, dilated lateral cerebral ventricle, and bilateral dilated ureter), and 13 skeletal variants affecting several skeletal districts. At 2.0 mL/kg-day no malformations were observed, but the incidence of two visceral variants, dilated lateral cerebral ventricle and bilateral dilated ureter, and one skeletal variant, reduced caudal segments, was increased.

Test substance :

2-Ethyl-1,3-hexanediol (CAS No. 94-96-2) (component)

Conclusion :

Under the conditions of this study, the test material was considered to be a weak developmental toxicant at 4.0 and 2.0 mL/kg/day, and 1 mL/kg/day was a "no-observed effect level" for developmental toxicity. As developmenatl toxiciity was oserved only in the presence of maternal toxicity (liver weight increase), the test material is not considered a specific developmental toxin.

Reliability : (1) valid without restriction

Published study, protocol similar to OECD guidelines.

23.12.2004 (16)

(1) BASF, MSDS for Oxoel 800, Ver 2 Druckdatum 27.09.2002

(2) Estimated by Toxicology and Regulatory Affiars (December 2003) using AOP Program (ver 1.90) as found in EPIWIN 3.05 Syracuse Research Cororation and EPA (April 2000).

(3) Estimated usng HYDROWIN 1,67 as found in EPIWIN 3.04 Syracuse Research Cororation and EPA. (April 2000).

(4) Astill BD, Deckardt K, Gembardt C, Gingell R, Guest D, Hodgson JR, Mellert W, Murphy SR, Tyler TR. Prechronic toxicity studies on 2-ethylhexanol in F334 rats and B6C3F1 mice. Fundam Appl Toxicol. 1996 29:31-9.

(5) BASF AG, Labor Okologie und Umweltanalytic: unpublished report, Prufung der biologischen Abbaubarkeit von Oxooel 800 in CO2 Entwicklungtest. Project Number 96/0418/22/1 7 Feb 1997.

(6) BASF Technical Data Sheet for EP-204 2-Ethylhexanol Heavies. Product Number 526158, Published December 2003

(7) Data found on NTP public database at http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm

(8) Determination of the acute effect of Oxo Oil 800 on the swimming ability of the water flea Daphnia magna STRAUS. Final Report Project Number 96/0418/50/2 BASF AG 10.07.1998.

(9) Developmental Toxicity of 2 Ethylhexanol (CAS NO. 104-76-7) in CD-1 Swiss Mice NTP Study: TER90029. Abstract available on the NTP web site and the entire report is available from NTIS.

(10) EQC Level 3 Model as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).

(11) Estimated by Toxicology and Regulatory Affairs, Freeburg IL 2004

(12) Estimated using HYDROWIN 1,67 as found in EPIWIN 3.05 Syracuse Research Cororation and EPA. (April 2000).

(13) J.C. Harris in Lyman W, Reehl, W and Rosenblat, D. Handbook of Chemical Property Estimation Methods. American Chemical Society, Washingotn D.C. 1990, page 7-6

(14) Laboratory Report, BASF Toxikologie, Study of the Acute Oral Toxicity to Rats. Substance 84/44, Oxool 800. 30 August 1984.

(15) MPBPWIN (v1.40) Program as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).

(16) Neeper-Bradley TL,Fisher LC, Butler BL, Ballantyne B Evaluation of the developmental toxicity potential of 2-ethyl-1,3-hexanediol in the rat by cutaneous application. J Toxicol Cutaneous Ocul Toxicol 1994;13(3):203-14

(17) Price CJ; Tyl RW; Marr MC; Myers CB; Morrissey RE; Heindel JJ; Schwetz BA Developmental toxicity evaluation of DEHP metabolites in Swiss mice. Teratology 1991 May;43(5):457

(18) Sage, M; and Sage, G. Vapor Pressure. in Handbook of Property Estimation Methods for Chemicals, RS Boethling and D Mackay eds. 2000, Lewis Publishers.

(19) Study of Oxoel 800 in an acute inhalation risk test (rats). BASF 84/44 30 May 1984.

(20) WSKOW program (v1.40) as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).