201-15345

Alcohols, C4, distn. residues

CAS Number 68551-11-1

A Variable Mixture Also Know as:

- Butanol Bottoms
- EP-202MP

U.S. EPA HPV Challenge Program Submission

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Executive Overview

EP-202MP (CAS no. 68551-11-1) is the name BASF Corporation uses in the United States for the high-boiling fraction from the hydroformylation of propene. CAS no. 68551-11-1 is a byproduct from the production of butyraldehyde or butanol and is known by several names in commerce including "Butanol Bottoms", the more specific name EP-202MP, and the TSCA Inventory description "1-Propene, hydroformylation products, high-boiling". EP-202MP is an amber colored clear liquid with a moderate organic odor and is a variable composition mixture containing about 10 different components at greater than 1% and generally, no single component greater than 20%. It can be used as a chemical solvent but much if it is burned for fuel value. As a result of the limited application of this material and the fact that it is produced in only one plant in the US, the potential for environmental release is limited. Likewise, due to these same factors and its low volatility, the possibility for human exposure is very limited. The chemistry involved in the genesis of EP-202MP is discussed in detail to understand what components are possible, and this information is used to conduct a hazard assessment of the material based on its known and possible components.

2-Ethylhexanol is an important component of the material and was selected, using scientific rationale, as the most representative material with sufficient data that would be an adequate surrogate to represent this variable mixture. Data on EP-202MP itself indicate that it is a biodegradable liquid with low-volatility. 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 less than 15 hours. Water solubility of the individual components ranges from less than 1 mg/L to about 6000 mg/L; overall, the water solubility is low. If released into the environment it is expected to distribute primarily to water and soil.

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 35 to 150 mg/L. Having limited solubility and good biodegradability also reduces 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 range from –0.48 to 5.17 with an average value of 2.4. This attribute combined with biodegradability and rapid metabolism indicate little propensity for bioaccumulation.

EP-202MP demonstrated an acute LD_{50} greater than 5000 mg/kg after oral gavage administration to rats of each sex. No repeated administration studies are available for EP-202MP; however, several of its major components have been tested. Data from subchronic oral and inhalation testing of 2-ethylhexanol were selected as appropriate surrogate data to estimate the repeated-dose hazard of EP-202MP. Based on these data, EP-202MP 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.

Potential genetic effects were assessed via examination of adequate data for most of the major components of EP-202MP. The weight of evidence indicated lack of mutagenic or clastogenic activity for components of EP-202MP. No structural alerts were identified for any of the untested known components. Based on the chemistry 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 (another surrogate that also encompasses the ester functionality of some EP-202MP components).

Lack of developmental toxicity was also indicated by the one-generation dietary reproduction study of di-2-ethylhexyl adipate where minor fetotoxicity (fetal weights) was observed at maternally toxic doses. In addition, the National Toxicology Program conducted a gavage-administration developmental toxicity study in mice with 2-ethylhexanol; developmental toxicity was not observed at the highest dose tested (194 mg/kg-day).

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 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. 68551-11-1 EP-202MP	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	N	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	Y	N	Y	N	Y	N	
Acute Invertebrate	Y	Y	N	Y	N	Y	N	
Acute Algae	Y	Y	N	Y	N	Y	N	
Toxicity								
Acute	Y	Y	?	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 hydroformylation of propene, CAS no. 68551-11-1, is known by several names in commerce including the more generic name "Butanol Bottoms" and the more specific name EP-202MP used by BASF to designate this particular byproduct. The TSCA Inventory refers to this material as "1-Propene, hydroformylation products, high-boiling" with the following description:

> A complex combination of hydrocarbons produced by the distillation of products from the hydroformylation of C3 to C15 alkenes. It consists predominantly of organic compounds such as aldehydes, alcohols, esters, ethers and carboxylic acids having carbon numbers in the range of C4-C16 and boiling in the range of approximately 143°C to 282°C.
>
> Unknown, Variable, Complex, Biological Flag: UVCB

The TSCA Inventory description above is broad, allowing for alkene feedstocks from three carbons to 15 carbons. The High Production Volume (HPV) mixture produced by BASF and described in this document is restricted to the high-boiling fraction derived from the hydroformylation of propene. In spite of this limitation, the TSCA UVCB flag (Unknown, Variable, Complex, Biological Flag) still applies, as this is an indeterminate mixture of chemicals some of which have not been definitively identified.

The objective of the hydroformylation reaction is to prepare aldehydes and alcohols one carbon longer than the feedstock from an alkene and carbon monoxide under reductive conditions using a catalyst. The chemistry is not highly specific and several products are formed by dimerization, partial oxidation and condensation. The crude reaction product is fractionally distilled to remove the desired aldehydes (butyraldehyde and isobutyraldehyde) or alcohols (butanol and isobutanol) that are the major products of the process. What is left behind after distillation is the "high-boiling" fraction and has been assigned the CAS no 68551-11-1 and, in the United States, BASF designates this chemical mixture as EP-202MP, which is the name used in this document. BASF practices this chemistry as a 2-step process with the first step being production of the aldehydes and the second step reduction of the aldehydes to alcohols. Distillation residues from both steps are combined to produce EP-202MP.

EP-202MP is an amber-colored clear liquid with a moderate organic odor (1). Industrial and commercial applications are listed as "chemical solvent"; however, most of the product is utilized for it heat value as a fuel. Estimated production of EP-202MP by BASF in the United States is in the range of 7 to 12 million pounds. United States production of the material is limited to one plant.

Production is in a closed continuous flow reaction system before storage in closed tanks. Shipping is limited to bulk transport by railcar 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 railcars and tank-trucks but is controlled by the use of personal protective equipment when handling the material outside of the closed manufacturing system. Potential exposure to EP-202MP is also limited by its low volatility; the two major components 2-Ethylhexenal and 2-Ethylhexanal, have estimated vapor pressures of about 3 and 0.6 hPa, respectively. In addition to low volatility, as an unsaturated aliphatic aldehyde,

the more volatile of the two major components is expected to have excellent odoriferous warning properties. If exposure occurs, the duration is expected to be short as this material is produced, stored and transported in closed systems. The potential for exposure is generally limited to sampling, connecting transport equipment and maintenance activities; all of which are short-term exposures.

The composition of EP-202MP is a critical aspect of this HPV analysis; thus, the chemistry of formation of EP-202MP and its typical composition is discussed in detail below in the "chemistry" section of this document.

Several physicochemical, fate and toxicity studies have been conducted with EP-202MP. These studies 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 (HPV) Challenge 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-202MP have not been conducted, data from studies of the major components or other surrogates are provided to fill the HPV endpoint data gaps. In some cases where calculated data are acceptable, a calculation based on the major components has been utilized. The use of acceptable surrogates and acceptable estimation methods are encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing cost and animal usage.

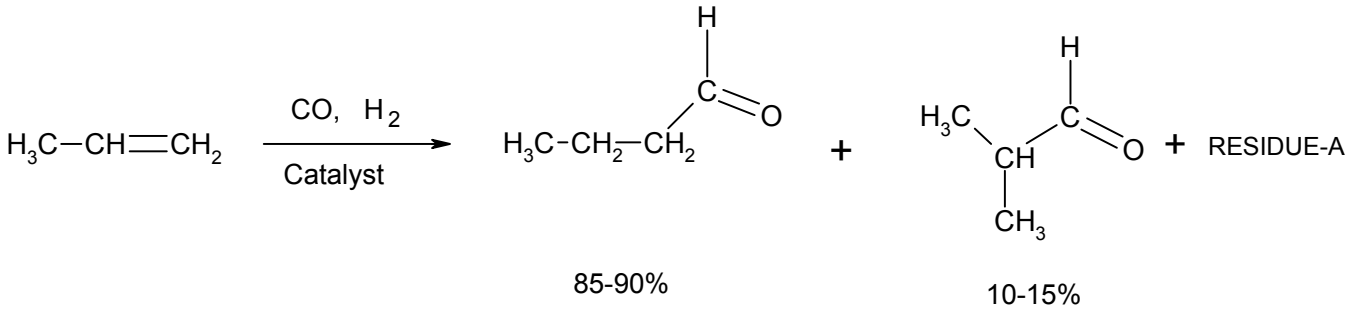
Chemistry

EP-202MP (CASNO 68551-11-1) is an indeterminate mixture of variable composition derived as a byproduct from a chemical process. To understand how this material relates to other mixtures and pure chemicals that have relevant data and to appreciate the potential range of various components, it is useful to comprehend the process and process variables that contribute to the production of this byproduct mixture.

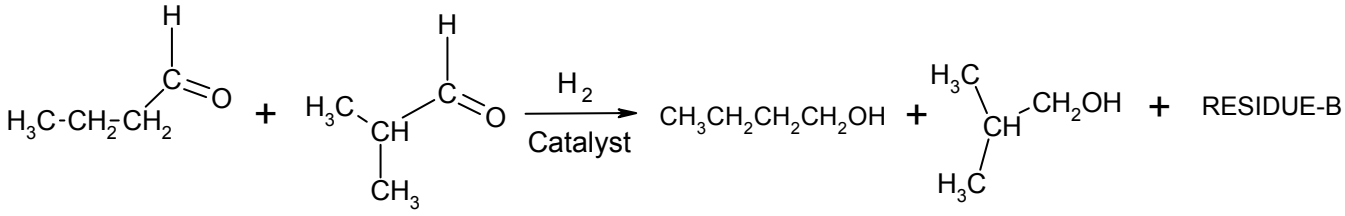
EP-202MP is a residue remaining from the oxo-process synthesis and distillation of butyraldehydes combined with a residue from the subsequent hydrogenation of butyraldehyde and distillation of the resulting butanol. In this particular process, propylene is used as a feedstock and reacted with carbon monoxide and hydrogen over a catalyst to cause carbon monoxide to add to the double bond on either the 1 or the 2 carbon of propylene. Addition to the 1-carbon gives n-butyraldehyde and addition to the 2-carbon gives isobutyraldehyde. Conditions are generally optimized to produce as much of the more valuable n-butyraldehyde as possible. Under the conditions used at BASF, the isobutyraldehyde content ranges from about 10 to 15% of the product. At the temperatures and pressures employed a small amount of the butyraldehyde undergoes condensation reactions (aldol-type) to produce higher molecular weight substances that can undergo reductive or oxidative reactions to give various alcohols and carboxylic acid. During the distillation phase of this continuous process, additional reactions may occur to build higher molecular weight compounds. The process continues in a separate step to produce butanol and isobutanol by catalytic reduction of the distilled aldehydes in different reactor. Similar to the carbonylation reaction, the aldehydes have the opportunity to undergo condensation reactions prior to reduction

producing small quantities of higher molecular weight materials. As the higher molecular weight compounds tend to be less volatile, they remain in the residues from the distillations that comprise EP-202MP.

The primary reaction of this hydroformylation process is:



In the production of EP-202MP, the "heavies" from distillation of the aldehydes are blended with the heavy fraction from the subsequent reduction of butyraldehydes to butanols.



The blend of the "heavies" (Residue-A and Residue-B) is called EP-202MP. The overall process is formally a hydroformylation reaction but it is broken up into two steps to optimize the production of the aldehydes and alcohols.

RESIDUE-A + RESIDUE-B = EP-202MP

In either of these reactions, the aldehydes (products in the first instance and starting materials in the second) are considered to be the primary chemically active material leading to the production of "heavies". Likewise, in each reaction both aldehydes and alcohols are present and the chemistry leading to production of higher molecular weight materials is considered similar.

Aldol type condensation reactions followed by redox reactions can occur to form C8 and larger compounds as shown in Figure 1. In addition to the structures shown, isomers of all three compounds can be formed from the crossed aldol reaction between butyraldehyde and isobutyraldehyde.

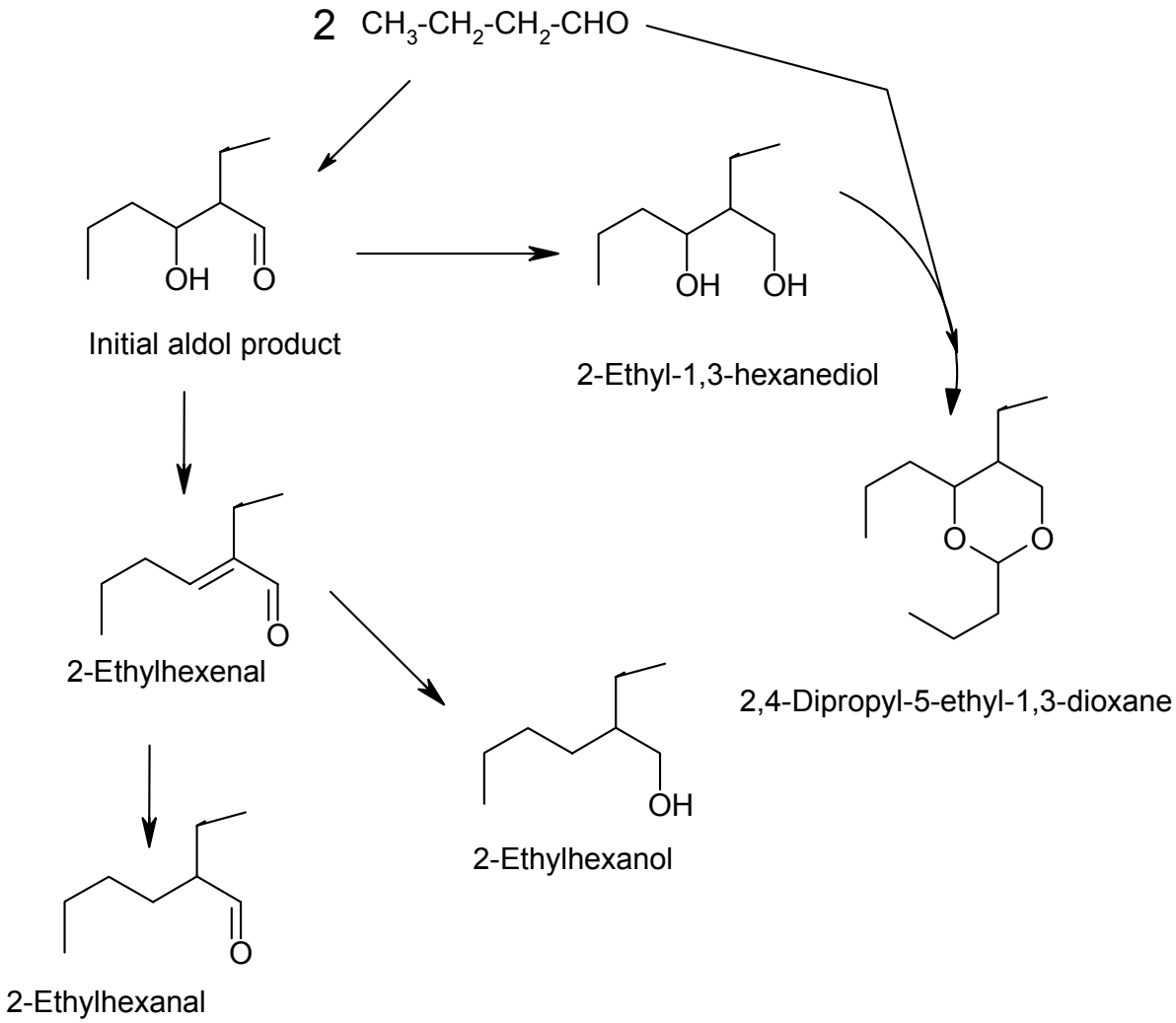


Figure 1. Genesis of EP-202MP C8 + Compounds

In addition to this series of reactions, simple redox chemistry and ester formation from carboxylic acids and alcohols will occur. The number of potential products is very large, accounting for the complexity of EP-202MP and the reason that many components remain unidentified. Table 1 gives a typical composition for the identified components of EP-202MP.

Chemical Components	CAS No.	Weight % (mean)
2-Ethylhexenal	645-62-5	10.33
2-Ethylhexanal	123-05-7	9.96
n-Butanol	71-36-3	6.77
2-Ethyl-1,3-hexanediol	94-96-2	5.32
2-Ethylhexyl-1,3-dibutyrate		4.12
2,4-Dipropyl-5-ethyl-1,3-dioxane		3.24
n-Butyl-n-butyrate	109-21-7	2.92
N-butyraldehyde	123-72-8	2.47
2-Ethylhexanol	104-76-7	1.57
Isobutanol	78-83-1	0.86
2-Ethylhexyl-butyrate	25415-84-3	0.45
Isobutyraldehyde	78-84-2	0.43
3,5-Diethyl-2-propyltetrahydropyran		0.14
4-Heptanol	589-55-9	0.11
2-Ethylhexyl-butyl ether	62625-25-6	0.08
Butyl butenyl ether		0.07
Isobutyl-n-butyrate	539-90-2	0.03
2-Methylbutanol	137-32-6	0.01
n-Butyl-isobutyrate	97-87-0	0.01
	TOTAL	48.89

Table 1. Typical Composition of EP-202MP (identified components)

Additional characterization work using analytical tools such as gas and liquid chromatography combined with mass spectrometry has been conducted to categorize some of the unknowns (Table 2).

EP-202MP Chemical Components	CAS No.	Weight % (range)
C4 Aldehydes		2-8
C4 Alcohols		10-15
C8 Esters		5-10
C8 Aldehydes		10-20
Others, C8 and heavier		50-60
Water		0.1-0.2

Table 2. Categories of Components in EP-202MP

In addition to this characterization, a ^{13}C-NMR spectrum was recorded to gain some assurance that the bulk product was composed of only aliphatic materials or if not, 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 in spite of it having a large percentage of components that have not been identified. The NMR allows some tentative identifications to be made and some rough estimates of the relative contribution of several types of molecules.

Tentative assignments of some of the carbon signals in a recent batch of EP-202MP is useful in assessing the variety of structures contained in this mixture and are provided in Table 3. It should be noted that the NMR data are primarily confirmatory of the other analysis and consideration of the likely chemical reactions and does not reveal any unanticipated components.

Chemical Shift (ppm)	Tentative Identification	Approx Relative Percent
203- 205	Aldehydes (2 compounds)	2-10% C8 units
170-200	Esters (2 compounds)	2-10 %
145-155	Olefin (1 compound) olefin carbons of α,β-unsaturated aldehyde	5-15%
95-105	Acetals or hindered ethers	5-15%
70-80	Alcohols (2°)	15-40%
60-70	Alcohols (1°)	20-50%

Table 3. Tentative Assignments of Carbon Signals in EP-202MP

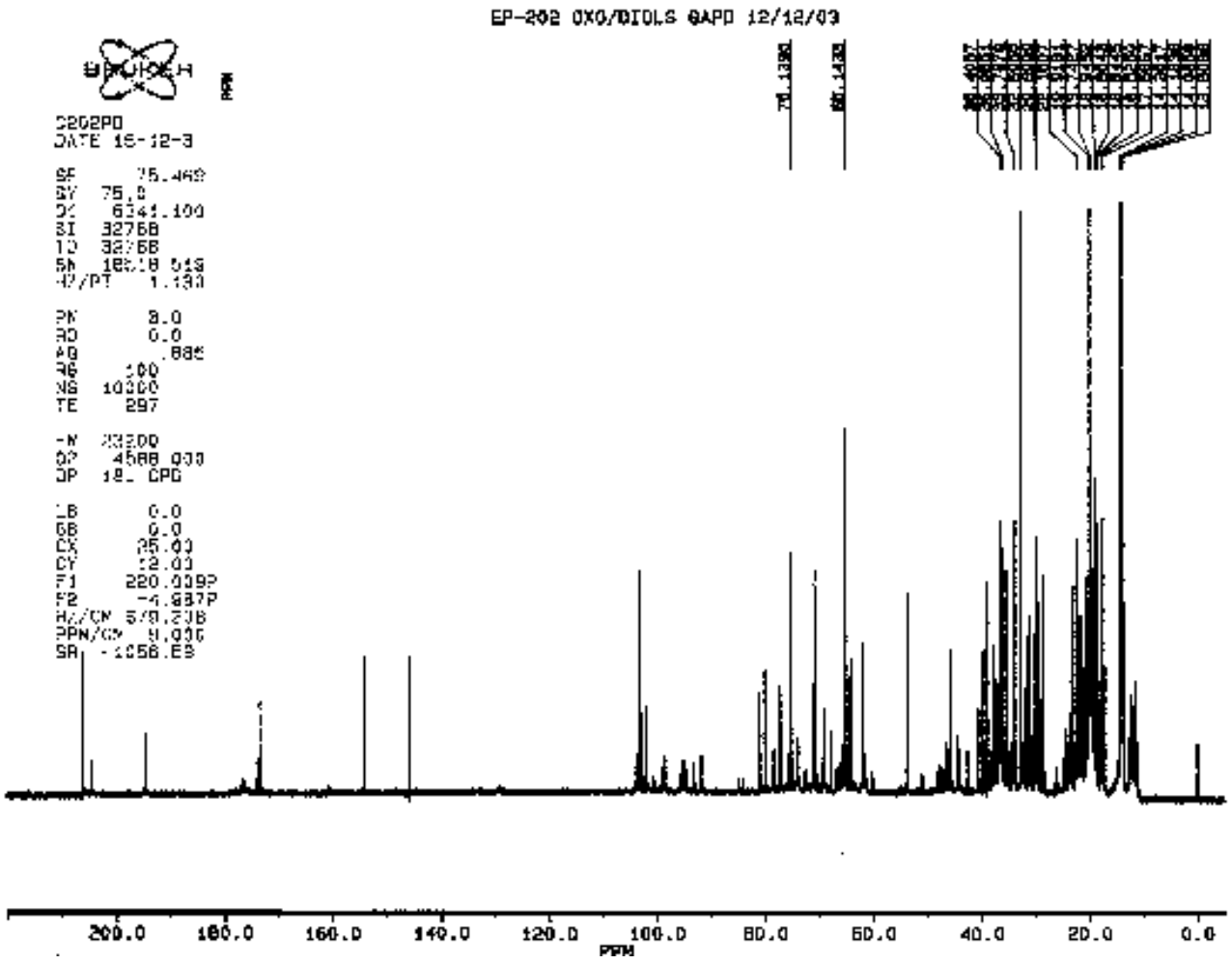


Figure 2. ^{13}C-NMR spectrum of EP-202MP

Physicochemical Data

Physicochemical data for EP-202MP are available from manufacturer's information and from EPIWIN estimates and are summarized in Table 4.

Melting Point	ca. –90˚ C (2)
Boiling Point	93° C (initial) @ 1013 hPa (2)
Vapor Pressure	ca. 1 – 5 hPa @ 25˚ C (3)
Partition Coefficient	Log $K_{o/w}$ = -0.48 – 5.17 (4)
Water Solubility	Variable, 0.5 – 6000 mg/L (4)

Table 4: Physicochemical Summary Data for EP-202MP

The freezing (melting) point and boiling point (initial) are measured properties for typical material as stated on the Technical Data Sheet for EP-202MP. Notice that only the approximate initial boiling point is given, as this is a material that undergoes fractional distillation as it boils.

A single octanol-water partition coefficient cannot be defined as this mixture has a variety of components that have varying hydrophobicities. To understand the potential distribution and bioaccumulative properties of EP-202MP, individual components must be considered. Table 5 contains the EPIWIN estimated log Ko/w for the nine 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-202MP, they represent a good cross section of the chemical classes that comprise EP-202MP and are considered representative of the entire sample (5). The $K_{o/w}$ spans from –0.48 for butyraldehyde to 5.17 for 2-ethylhexyl-1,3-dibutyrate. Although two of the materials have $K_{o/w}$ values greater then 3, that indicate bioaccumulation is possible, the one with the highest $K_{o/w}$ is an ester, which is expected to be both biodegradable and easily converted by esterases in man and animals to 2-ethyl-1,3-hexanediol and butyric acid that have lower $K_{o/w}$ values. The only structures that are of concern from a persistence and potentially bioaccumulative perspective are the simple ethers (e.g. ethylhexyl-butyl ether at less than 0.1% of the material) and the cyclic substituted 1,3-dioxanes (about 3% of the mixture).

Component	SMILES	log Kow*	H_2O Sol* (mg/L)
2-Ethylhexenal	CCCC=C(CC)C=O	2.62 c	586 e
2-Ethylhexanal	CCCCC(CC)C=O	2.71 c	108 c
n-Butanol	CCCCO	0.88 e	6320 e
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	1.60 c	4200 e
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	5.17 c	0.56 c
n-Butyl-n-butyrate	CCCC(=O)OCCCC	2.83 c	309 c
n-Butyraldehyde	CCCC=O	-0.48 e	238 e
2,4-Dipropyl-5-ethyl-1,3-dioxane	C(CCC)1C(CC)COC(CCC)O1	3.89 c	20.7 c
2-Ethylhexanol	CCCCC(CC)CO	2.73 c	880 e
* e = experimental value from SRC database, c = calculated value using EPIWIN			

Table 5: Experimental and Calculated Octanol-Water Partitions Coefficients for EP-202MP

Vapor pressure for EP-202MP is also a variable parameter. It depends initially on the vapor pressure and physicochemical interactions (with other components) of the most volatile components and, as the mixture evaporates and loses the more volatile components, the vapor pressure will decrease. For the purpose of this table for bulk material, the vapor pressure was estimated from the initial boiling point using chemical principles (see robust summary). In the environment after dispersal, individual vapor pressures are a determinant of distribution and individual vapor pressures were taken into consideration in the fugacity calculations.

Water solubility is dependent on the solubility of individual components and on the bulk properties of the material as a whole; in the presence of an organic liquid phase the partition coefficient is as important as the solubility. In addition, with any partially water-soluble mixture, cosolvent effects are expected to play an important role. As this is a variable mixture and cosolvent effects are difficult to model, the experimental or calculated water solubilities are used as reference values, with the understanding that under various conditions the effective solubility could be different. Considering that the composition is mostly higher molecular weight 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

Biodegradation potential of the “heavy fraction” from the butanol distillation has been determined using oxygen uptake measured with a respirometer (OECD guideline 301C) (6). This material was found to be greater than 60%

biodegradable. Although it is not clear if this result meets the OECD "readily biodegradable" criteria, it is apparent that biodegradability is good on this sample of material. This information is consistent with the structures of the most prevalent compounds; however, it should be taken into consideration that some of the components with linear and cyclic 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.

2-Ethylhexanol is considered a reasonable surrogate for the product due to its branched structure and oxidation state. It is known to be biodegradable giving either 55% or 68% biodegradation in 17 days in a Directive 84/449/EEC, C.5 "Biotic degradation – modified Sturm test" (7) and 88% in 17 days in an EEC Directive 79–831 Annex V Part C (1984): Methods for the determination of ecotoxicity. Degradation – Biotic Degradation, Manometric Respirometry test (8). In an inherent biodegradation test (OECD-302B guideline), 2-ethylhexanol was found to degrade more than 95% in only 5 days (9).

Although there are some unresolved issues over the test material meeting the OECD readily biodegradable criteria and the exact extent of 2-ethylhexanol's biodegradation, overall, there is high confidence that EP-202MP is biodegradable in the environment. It must also be kept in mind that actual testing would involve testing of a variable mixture in a inconsistent test system (source and activity of inoculum will differ); therefore, the existing information indicating relatively facile biodegradation of major components combined with the expectation that ethers and more highly branched structures will biodegrade more slowly is sufficient to meet the requirements of the HPV screening test program.

Water Stability

Water stability has been estimated for the major components of EP-202MP. Most of the components do not contain a water-reactive or hydrolysable group. The aliphatic alcohols and aliphatic ethers that make up the bulk of EP-202MP are considered water stable for this reason (10). The materials that are potentially hydrolysable are the two aliphatic esters. The esters' structures were entered into the HYDROWIN (v1.67) program to estimate hydrolysis rates (see robust summary for details). This program gave estimates for the second order hydrolysis rate with hydroxyl ion. These rate constants were used to estimate the half-life of these two esters in water at pH 7 and pH 8. The results are shown in Table 6.

Water Stability of EP 202	K_b (estimated)	Half-life (years)	
Component	(L/mol-sec)	pH 7.0	pH 8.0
2-Ethylhexenal	0	>> 1	> 1
2-Ethylhexanal	0	>> 1	> 1
n-Butanol	0	>> 1	> 1
2-Ethyl-1,3-hexanediol	0	>> 1	> 1
2-Ethylhexyl-1,3-dibutyrate	0.0015	6.2	0.62
n-Butyl-n-butyrate	0.053	4.1	0.41
n-Butyraldehyde	0	>> 1	> 1
2,4-Dipropyl-5-ethyl-1,3-dioxane	0	>> 1	> 1
2-Ethylhexanol	0	>> 1	> 1

Table 6. Water Stability of EP-202MP Components

It should be noted that although the aldehydes are estimated to be essentially indefinitely stable in pure water solution (they typically exist in a hydrated form) they will react with organic material found in lakes and waterways and will thus exhibit a shorter abiotic degradation half-life than predicted on only the basis of hydrolysis. In addition, it is estimated that all of the components will biodegrade in natural waters far faster than they will undergo abiotic hydrolysis.

Photodegradation

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 nine most prevalent (greater than 1%) 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 6.2×10^{-12} to 50.7×10^{-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-202MP for reaction with hydroxyl radical, the estimated half-life of EP-202MP vapor in air is approximately 2 to 8 hours. The full details of the calculations are given in the robust summaries and the table below provides a summary of the results.

Regarding the components at less than one percent and the unidentified components, as they have similar empirical formulas (based on the NMR and potential chemical reactions), the reaction rate constants for hydroxyl

radical are going to be similar (see robust summary for example calculations showing the influence of structure on reactivity with hydroxyl radical) indicating rapid photodegradation.

EP-202MP Component	Results of AOP v 1.09 Hydroxyl Radical Reaction Prediction			AOP Ozone Prediction
	Rate Constant ($x10^{12}$ cm/molec-sec)		Half-life (hrs)	Half-life (hrs)
	Calculated	Experimental		
2-Ethylhexenal	49.99	n	2.6	23.2
2-Ethylhexanal	33.98	n	3.8	nr
n-Butanol	6.89	8.75	14.1*	nr
2-Ethyl-1,3-hexanediol	22.23	n	5.8	nr
2-Ethylhexyl-1,3-dibutyrate	17.53	n	7.3	nr
n-Butyl-n-butyrate	6.24	10.6	12.1*	nr
n-Butyraldehyde	25.43	23.5	5.47*	nr
2,4-Dipropyl-5-ethyl-1,3-dioxane	50.69	n	2.5	nr
2-Ethylhexanol	13.23	n	9.7	nr
	n = not found, nr = no reaction			

Table 7. Summary of Photodegradation Estimates

As the calculations show, the primary reaction for this series of material is hydrogen abstraction and the rate increases linearly as the number of abstractable hydrogens increase (see robust summaries for examples). The ether moiety activates adjacent hydrogen atoms toward radical abstraction while the ester is a deactivating influence. Based on the structures, reaction with ozone will not be important. 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-202MP in the environment was estimated using the MacKay EQC level III model with standard defaults found 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 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-202MP is a function of the partial pressures of each component, it is more appropriate to use the individual EPIWIN predicted vapor pressure (or the individual measured vapor pressure) for each component in these calculations. Likewise, individual predicted values for log $K_{o/w}$, $K_{o/c}$, and half-lives were utilized. The biodegradation half-lives that were used were EPIWIN generated but were individually 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 table is shown below. The components evaluated are representative of the full

spectrum of components contained in EP-202MP and include alcohols, aldehydes, an α,β-unsaturated aldehyde, esters and a substituted dioxane. What is apparent is that the components distribute primarily to water and soil with little in the air or sediment except for the two esters, with n-butyl butyrate being more volatile and 2-ethylhexyl-1,3-dibutyrate distributing in sediment to a significant extent.

EP-202MP Component	%	SMILES	Distribution (Percent)			
			Air	Water	Soil	Sediment
2-Ethylhexenal	10.33	CCCC=C(CC)C=O	1.39	34.7	63.7	0.216
2-Ethylhexanal	9.96	CCCCC(CC)C=O	2.58	34.1	63.0	0.241
n-Butanol	6.77	CCCCO	5.91	49.5	44.5	0.0782
2-Ethyl-1,3-hexanediol	5.32	CCCC(O)C(CC)CO	0.34	38.6	61.0	0.0859
2-Ethylhexyl-1,3-dibutyrate	4.12	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	1.59	27.7	48.5	22.2
2,4-Dipropyl-5-ethyl-1,3-dioxane	3.24	C(CCC)1C(CC)COC(CCC)O1	0.604	19.7	77.6	2.13
n-Butyl-n-butyrate	2.92	CCCC(=O)OCCCC	7.8	35.2	56.8	0.208
n-Butyraldehyde	2.47	CCCC=O	3.68	53.5	42.7	0.095
2-Ethylhexanol	1.57	CCCCC(CC)CO	4.24	41.2	54.3	0.216

Table 8: Theoretical Distribution (Fugacity) of EP-202MP in the environment

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

Ecotoxicity

No studies have been conducted on the aquatic toxicity of EP-202MP as a mixture; however, a considerable number of studies have been conducted on many of the major components and others can be reliably estimated using ECOSAR and the appropriate model. These are shown in Table 9.

Aquatic Toxicity of EP-202MP Components (all values in mg/L)						
	2-Ethylhexenal	2-Ethylhexanal	n-Butanol	Diol^	Butyraldehyde	2-Ethylhexanol
Approx. percent of EP-202MP	10+%	10%	7%	6%	3%	2%
Fish, 96-hr LC_{50}	6.0 (11)	8 (12)	> 1000 (13)	257*	25.8 (14)	17-30 (15)
Daphnia, 48 hour EC_{50}	20 (16)	11.5 (17)	> 1000 (13)	268*	195# (14)	39 (15)
Algae, 72 or 96 hour EC_{50}	19.3 (18)	52 (17)	> 100 (13)	164*	83 (14)	10-20 (15)
* Estimated using ECOSAR (19) # 24-Hour value			^ diol = 2-Ethyl-1,3-hexanediol			

Table 9: Aquatic Toxicity of EP-202MP Components.

Determination and estimation of the actual ecotoxicity values and the actual solubility of EP-202MP are complicated by the fact that it is a variable mixture and actual environmental conditions are not known. The two major components are aldehydes that are anticipated to have "excess" toxicity to aquatic species over materials such as alcohols that are considered "neutral organics" in modeling (20). Based on this reasoning and the low solubility of neutral organics with higher $K_{o/w}$ values (including the esters in EP-202MP), the aquatic toxicity of EP-202MP will primarily be a function of the aldehyde components and primarily the two in highest concentration, specifically 2-ethylhexenal and 2-ethylhexanal. If these represent about 20 % of the mixture, a rough estimate of the toxicity in a system where all the aldehydes distribute into the water column in an available form would be based on 20 % of the acute value for the species, or:

- Fish ~35 mg/L
- Daphnids ~80 mg/L
- Green Algae ~150 mg/L

Considering that it is unlikely the toxic components will partition fully to the water column under most conditions, this is considered to be a conservative estimate for the overall aquatic toxicity of EP-202MP under actual conditions that might be encountered. It can be concluded that EP-202MP has a low to moderate potential for aquatic toxicity that is further moderated by the high biodegradability and chemical reactivity of the toxic components.

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

Health Effects

An acute oral study has been conducted on EP-202MP showing low acute toxicity. Several studies have been conducted on components of EP-202MP; these cover repeat dose and developmental toxicity of various components. The most relevant component is considered to be 2-ethylhexanol because of its metabolic link to most of the C8 compounds and even to some of the C4 compounds.

Metabolic Considerations

If one examines the spectrum of components in EP-202MP and considers the expected metabolic fate of each component, it becomes apparent that there metabolic relationships and/or potential biochemical pathways connecting many of the major components. Figure 3 presents a depiction of some of the possible biochemical connections of the EP-202MP components. While it is known that 2-ethylhexanol is extensively oxidatively metabolized, only the metabolites on the first line are definitively known to be in the 2-ethylhexanol metabolic pathway by virtue of the demonstrated urinary excretion of 2-ethylhexanoic acid (21). Nevertheless, these are all known pathways.

Considering the common pathways, it is a reasonable approach to use data from 2-ethylhexanol as a surrogate for systemic health effects from EP-202MP. Any “point of contact” effects that might be associated with administration of a reactive material, such as an aldehyde, would be excluded from this surrogate approach but for systemic toxicities (e.g. developmental effects), 2-ethylhexanol would appear to be a reasonable surrogate on metabolic grounds.

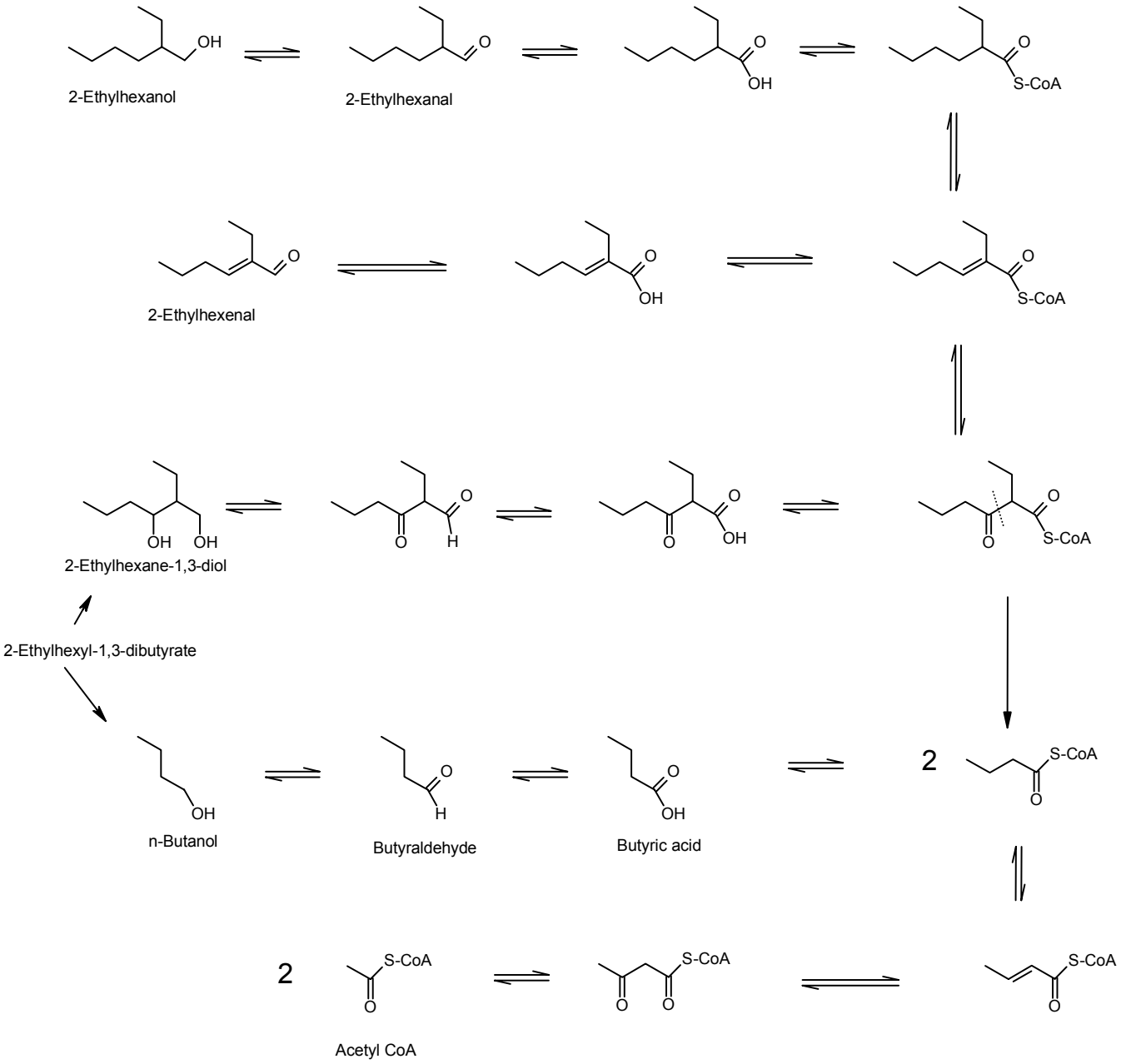


Figure 3. Putative Metabolic Interconversions of EP-202MP Components

Acute Toxicity

Oral Exposure

The oral LD_{50} of EP-202MP (tested as the butanol distillation heavy fraction, known as Oxooel 740[i]) was determined to be greater than 5,000 mg/kg in Wistar rats of each sex. In this guideline study, Wistar rats were dosed at 2000 or 5000 mg/kg and observed for 14 days. Only one high-dose male died. High-dose males showed clinical signs of intoxication more strongly than females. No specific target organ was identified (22).

Inhalation Exposure

A subchronic inhalation study using essentially saturation concentrations of 2-ethylhexanol vapors (120 ppm) has been conducted with no mortality after 13-weeks of exposure for 6 hours a day (30).

The aldehyde components are potentially inhalation hazards but they are such strong respiratory irritants that significant exposure of workers is considered unlikely (23).

Dermal Exposure

Dermally administered 2-ethylhexanol was evaluated for developmental toxicity using three groups of 25 pregnant female Fischer 344 rats that were treated cutaneously with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg-day (0, 250, 830 or 2,500 mg/kg-day) for 6 hours per day on gestation days 6 through 15 (24). No maternal deaths occurred but some maternal toxicity was apparent in that maternal weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals.

The dermal LD_{50} of 2-ethylhexanal (123–05–7) has been determined to be 5040 mg/kg in rabbits (25) and greater than 20,000 mg/kg for guinea pigs (26). As this material is one of the major components of EP-202MP and a member of the aldehyde family (which is considered to be the category of materials most likely responsible for any toxic effects of EP-202MP), this information reduces concern for the dermal hazard of EP-202MP.

Butyraldehyde, another component of concern for dermal toxicity due to its lower molecular weight and moderate $K_{o/w}$, has been found to be relatively nontoxic by skin administration. Skog found the dermal LD_{50} of butyraldehyde to be greater than 20,000 mg/kg for guinea pigs (27).

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i Oxooel 740 is the BASF designation for the heavy fraction from the distillation of the butanols. It was referred to as ‘Residue-B” earlier in this document and it is considered to have a very similar composition to “Residue-A”. Residue-B (Oxooel 740) comprises approximately 30% of EP-202MP.

Recommendation: No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although not all of the available studies meet the requirements of the current OECD guidelines, the weight of evidence shows that the oral and inhalation toxicity is very low. Likewise, the limited study of dermal toxicity provides support for low hazard by this route. 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.

Repeat Dose Toxicity

Oral Exposure

Repeated dose studies are available for a few of the components of EP-202MP; however, because of the metabolic commonality of probably pathways, 2-ethylhexanol was selected as the surrogate chemical of choice for assessing potential repeated dose toxicity of EP-202MP.

Recently conducted 13-week (28) and 2-year (29) studies are available for 2-ethylhexanol by oral gavage. In the 13-week study, groups of 10 rats 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 small but statistically significant ($p < 0.01$) reduction in weight gain in rats of each sex. Target organs were the liver and forestomach. There was a slight increase in relative testis weight at 500 mg/kg but this was not correlated with any morphological changes. Reduced relative ovarian weight was seen at 250 mg/kg but did not occur at 500 mg/kg and there was no morphological correlate; thus, it is considered incidental. It is concluded that 125 mg/kg was a NOAEL based on organ weight changes at 250 mg/kg. The primary "adverse" effect was peroxisome proliferation. Results of the 2-year study were similar in that gavage dosing of 500 mg/kg to rats was found to be associated with increased mortality (52%), liver lesions, and increase in relative testis weight. 2-Ethylhexanol was not considered carcinogenic. Significant increases in stomach, kidney and brain relative weights were observed in male rats at 150 mg/kg 2-ethylhexanol. Female rats had significantly increased stomach, liver, kidney and brain relative weights at the 150 and 500 mg/kg doses without histopathological changes. The 50-mg/kg dose level was a NOAEL.

A 90-day subchronic inhalation study of 2-ethylhexanol has also been recently published (30). 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.

Some repeated-dose testing has been conducted on other major components An OECD 412 Guideline inhalation study using Fisher rats has been conducted on 2-ethylhexanal but the available information is not sufficient to draw firm conclusions (31). What is available is that 250 ppm 6 h/day for 28 days was a LOAEL associated with reduction in weight gain and increased testes weights but few other effects. The NOAEL appears to be 100 ppm.

Several repeated dose studies have been conducted on n-butanol (32). Details are sparse but it would appear that n-butanol is not excessively toxic by inhalation after repeated doses and would contribute little to the toxicity of EP-202MP.

Recommendation: No additional repeated-dose studies are recommended. The available inhalation study adequately fills 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.

Genetic Toxicology in vitro

The prime surrogate, 2-ethylhexanol has undergone extensive genotoxicity testing with uniformly negative results. Some of these studies are listed in Table 10. Robust summaries for an Ames test (HPV mutation endpoint) and a chromosome aberration test (HPV chromosome damage endpoint) were prepared and are presented in the appendix. These were selected as representative studies based on high reliability scores for the studies and the availability of data for review and summarization.

Component	Test System	Result	Ref
2-Ethylhexanol	Ames Test [RS]	neg	33
	Ames Tests (multiple)	neg	34, 35, 36, & others
	In vitro CA [RS]	neg	33
	In vitro SCE	neg	33
	HGPRT assay (CHO cells)	neg	37
	Mouse lymphoma assay	neg	38
	Mouse micronucleus (in vivo)	neg	39
	Many others	neg	40
2-Ethylhexenal	Ames test	neg	41, 42
2-Ethylhexanal	Ames test	neg	43
n-Butanol	Ames test (multiple)	neg	44, 45
	CA in human lymphocytes	neg	46
	SCE (multiple)	neg	47, 48
	Mouse micronucleus (in vivo)	neg	49
Butyraldehyde	Ames test (multiple)	neg	50, 51, 52, 53
	CA in CHO cells	neg	54
	HGPRT	pos	55
	SCE in CHO cells	pos	54
	SCE in human lymphocytes	neg	56
	Drosophila SLRL test	neg	57, 58

Table 10. Genotoxicity of EP-202MP Components

Most of the available data on the major components that have obtainable data are summarized in Table 10. The materials without data are the esters and the dioxane, which are compounds that do not have any structural alerts that would suggest genotoxic activity. The aldehydes and the α, β-unsaturated compound 2-ethylhexenal, which are of the most concern relative to potential genotoxicity from an SAR perspective, have negative genotoxicity test data with the exception of a few positive results having been reported for butyraldehyde. Even for butyraldehyde, the weight of the evidence, when taken as a whole, indicates little genotoxic hazard. The minor identified components (i.e., < 1%) are basically of similar structures and there is no reason to anticipate any genotoxicity activity from the minor identified components. The carbon-13 NMR analysis also indicates the unidentified components have similar structural characteristics and are therefore considered to represent a low genotoxic hazard. In summary, it is concluded that EP-202MP has minimal genotoxic hazard *in vitro*.

Genetic Toxicology in vivo

Some *in vivo* genotoxicity studies have been conducted on the components of EP-202MP and representative results are shown in Table 10. The *in vivo* studies support the *in vitro* data indicating a minimal genotoxic hazard for EP-202MP.

Recommendation: The SIDS requirement for genetic testing has been met for both point mutation and clastogenic effects via the data summarized in Table 10. No additional testing is recommended for this variable complex mixture.

Reproductive Toxicity

Although no studies of the EP-202MP product 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-202MP, 2-ethylhexanol is considered to be an adequate surrogate for this mixture.

A formal reproductive toxicity study of 2-ethylhexanol was not found however there are modern 13-week and chronic studies in which the reproductive organs were evaluated and, aside from an increase in relative testes weights at high doses without corresponding histopathological changes, there were no effects on reproductive organs at the highest dose tested (500 mg/kg)(see repeat dose toxicity). In addition to this evaluation there is a negative developmental toxicity study in mice (see developmental toxicity section). 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 2-ethylhexanol and thus EP-202MP 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 (59). In a one-generation reproductive study (60), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets at the same levels (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, 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. In addition a fertility study on diethylhexyl adipate has been conducted demonstrating lack of effects on reproductive function in the rat.

Recommendation: No additional reproductive testing is recommended.

Developmental Toxicity

Developmental toxicity studies of 2-ethylhexanol have been conducted for the purpose of safety evaluation. In addition, di-2-ethylhexyladipate, which is also an excellent surrogate for EP-202MP, has been evaluated for developmental toxicity.

The National Toxicology Program conducted a developmental toxicity study on 2-ethylhexanol in mice (61, 62). 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 or 194 mg/kg-day) in 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 toxicity was 194 mg/kg-day

Dermally administered 2-ethylhexanol was evaluated for developmental toxicity using three groups of 25 pregnant female Fischer 344 rats that were dermally treated with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg/day (0, 250, 830 or 2,500 mg/kg-day) for 6 hours per day on gestation days 6 through 15 (63). 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 post-implantation 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 can be concluded that 2-ethylhexanol has no activity as a developmental toxin by the dermal route in rats.

As discussed earlier (vide ante) another surrogate chemical for use in assessing the toxicity of EP-202MP diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol) has been evaluated for developmental toxicity. DEHA is rapidly absorbed by rodents and converted to 2-ethylhexanol (64). In a one-generation reproductive study (65), 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 corresponding to 0, 19, 118 or 747 mg/kg-day 2-EH). 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 at maternally toxic doses was associated with only minor manifestations of fetal toxicity. The developmental and maternal NOAEL was 170 mg/kg-day.

Recommendation: No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental toxicity of this material.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that available information on EP-202MP and/or its components fills all of the requirements for physicochemical parameters, fate information, aquatic toxicity and mammalian toxicity. Although all available studies do not meet all the requirements of the current OECD guidelines, taken together the information provides a reliable hazard assessment for this variable mixture. In addition, the potential for exposure of this material to man and the environment is very limited due to its production at only one U.S site in closed systems, low volatility, few applications (*i.e*., use primarily limited to fuel value) and good warning properties. The possibility of human exposure is considered to be limited to minor dermal exposure to this low toxicity variable mixture of chemicals.

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