Reference 27

Surrogate data used for Schedule 6 notification

Human Health Endpoints For

Eicosanol, manuf. of distn., residues (2682937-26-2)

Introduction

This document sets out the justification to use surrogate data to fulfill the Health toxicity end-point requirements for a Schedule 6 notification of Eicosanol, manuf. of distn., residues (2682937-26-2). These requirements are listed below.

- Acute mammalian oral toxicity
- Acute mammalian dermal or inhalation toxicity
- Skin irritation
- Skin sensitization
- Repeated dose mammalian toxicity test (at least 28 days)
- In vitro gene mutation (e.g. Ames test)
- In vitro mammalian chromosomal aberrations
- In vivo mammalian chromosomal aberrations or gene mutation

As mentioned in 8.4.3 of the, Guidance Document for the Notification and Testing of New Chemicals and Polymers Draft: March 2021, surrogate data may be used to fulfill data requirements for which experimental data is not available. This use of surrogate data negates the need to conduct additional animal studies to meet the notification data requirements for this substance.

Composition of the notified and surrogate substances

The notified substance, a residual alcohol product, is a by-product of the alcohols manufacturing process. It is a UVCB substance that consists of several linear long chain alcohols, predominantly from C20 to C28. Eicosanol-1-ol (C20) ≤ 10%, docosanol-1-ol (C22) 45-65%, tetracosan-1-ol (C24) 19-31%, hexacoral-o-l (C26) 9-17%, and octacosan-1-ol (C28) ≤ 9% are the major components. These substances make up over 80% of its composition. Other constituents include, to a much lesser extent, secondary long chain alcohols and complex mixtures of long chain carboxylate esters and other classes of components that are described elsewhere in this notification.

There is considerable overlap in the structural nature of the components found in the notified and surrogate substances. Surrogates 1,2, 4 and 6 stand out as they contain considerable amounts of the same type of long chain normal alcohols found in the notified substance. The carbon chain lengths of these alcohols vary but overlap with that of the notified substance. Surrogate substances 3 and 5 are distinct in that they, like the notified substance, are residual alcohols (produced because of a final distillation) and contain other types of constituents in addition to the normal long chain alcohols found in the notified substance. Speciation of these components is only practical down to the level of the types of components which includes secondary alcohols, carboxylate esters, ethers, and other long chain types of components described elsewhere.

Surrogate 5 is further distinguished by its content that consists of lower amounts of normal alcohols but higher proportions of the other classes of components found in the notified substance. The inclusion of data from surrogate 5 provides the ability to characterize the potential influence of these distinctive classes of components on the overall toxicological character of the notified substance.

Representative structures of the different classes of constituents for both the notified and surrogate substances are given in a separate spreadsheet provided in this notification. Inspection of this spreadsheet reveals that the components of the notified and surrogate substances share significant structural and compositional similarities.

Available surrogate human health data

The similarity in the composition of the notified and surrogate substances allows the data available on surrogate substances to be used to fulfill the data requirements for this notification. The following table shows the information available for the surrogate substances.

Human Health Endpoint (surrogate substance number)	**Eicosanol, C20 alcohol (1)**	**Docosanol Behenyl, C22 alcohol (2)**	Alcohols, C16-18 alcs. manuf. (68603-17-8) (3)	Mixture of hexadecanol and octadecanol (4)	Alcohols, C18-22, distn. Residues, 1160164-88-4 (5)	Mixture of Eicosanol and Docosanol (6)
Acute mammalian oral toxicity	LD50, > 10,000 mg/kg (ref 59)	LD50, > 10,000 mg/kg (ref 29)	LD50, > 12,600 mg/kg (ref 31)	LD50, > 10,000 mg/kg (ref 30)	LD50, > 2,000 mg/kg (ref 48)	ND
Acute Toxicity: Dermal	ND	ND	ND	LD50, > 10,000 mg/kg (ref 30)	LD50, > 2,000 mg/kg (ref 49)	ND

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Acute Toxicity: Inhalation	ND	ND	ND	No deaths at saturated atmosphere (ref 30)	ND	ND
Skin Irritation	ND	Not irritating (ref 60)	ND	Not irritating (re 30)	Not irritating (ref 50)	ND
Skin Sensitization	ND	ND	ND	ND	Not sensitizing (ref 51)	Not sensitizing (ref 35)
Repeated dose mammalian toxicity test	ND	NOAEL > 1000 and 2000 mg/kg (26 weeks, in rats and dogs, respectively); (ref 47)	NOAEL > 1000 mg/kg (ref 34)	ND	90-day NOAEL 1000 mg/kg (ref 52)	ND
In vitro gene mutation (e.g. Ames test)	ND	Negative (ref 47)	Negative (ref 56)	ND	Negative (ref 53)	ND
In vitro mammalian chromosomal aberrations	ND	Negative (ref 47)	Negative (ref 57)	ND	Negative (ref 54)	ND

Human Health Endpoint (surrogate substance number)	**Eicosanol, C20 alcohol (1)**	**Docosanol Behenyl, C22 alcohol (2)**	Alcohols, C16-18 alcs. manuf. (68603-17-8) (3)	Mixture of hexadecanol and octadecanol (4)	Alcohols, C18-22, distn. Residues, 1160164-88-4 (5)	Mixture of Eicosanol and Docosanol (6)
In vitro mammalian mutagenicity	ND	Negative (ref 47)	Negative (mouse lymphoma) (ref 58)	ND	Negative (ref 55)	ND
In vivo mammalian mutagenicity test	ND	Negative (ref 47)	ND	ND	ND	ND

Use of surrogate data to fulfill each required human health endpoint

The anticipated toxicological profile of the notified substance as characterized by the results of studies on the surrogate substances is summarized below.

Acute toxicity, irritation, and sensitization data

General considerations

There is considerable overlap in the structural nature of the components found in the notified and surrogate substances. Surrogates 1,2, 4 and 6 stand out as they contain considerable amounts of the same type of long chain normal alcohols found in the notified substance. The carbon chain lengths of these alcohols vary but overlap with that of the notified substance. Surrogate substances 3 and 5 are distinct in that they are residual alcohols (produced because of a final distillation) and contain other types of constituents in addition to the normal long chain alcohols found in the notified substance. Speciation of these components is only practical down to the level of the types of components which includes secondary alcohols, carboxylate esters, ethers, and other long chain types of components described elsewhere.

Surrogate 5 is further distinguished by its content that consists of lower amounts of normal alcohols but higher proportions of the other classes of components found in the notified substance. The inclusion of data from surrogate 5 provides the ability to characterize the potential influence of these distinctive classes of components on the overall toxicological character of the notified substance.

Representative structures of the different classes of constituents for both the notified and surrogate substances are given in a separate spreadsheet provided in this notification. Inspection of this spreadsheet reveals that the components of the notified and surrogate substances share significant structural and compositional similarities.

Collectively, these results of these studies suggest that a low toxicity potency and an absence irritative or sensitization hazard can be anticipated for the notified substance. The representative results of the study on docosanol provides convincing support the idea that the long chain linear alcohols of the type found in the notified substance are of sufficiently low toxic potency to be regarded as practically nontoxic. The results of studies of these two residue products are supportive of the expectation that the other types of substances found in the notified substances besides the long chain alcohols of the docosanol-like type, are not expected to exert an adverse impact on toxicity as exhibited by the lack of adverse impact on toxicity even though present at higher levels than that found in the notified substance.

Further details for each of these endpoints is presented below.

Acute mammalian oral toxicity

The acute oral toxicity of the notified substance can be is estimated based on the results from studies on several of the surrogate substances shown in the table. A possible upper end of the estimated range of > 12,500 mg/kg for the notified is suggested by the results on surrogate 3, one of the surrogate alcohols that is also a residual alcohol like the notified substance. This value is within the range of results obtained for surrogates 2, 3 and 4. The acute oral toxicity of docosanol-1-ol (surrogate 2) is LD_{50} >10,000 mg/kg. The value of > 2000 mg/kg obtained for the other residual alcohol surrogate, number 5, reflects the upper dose used in the study and is not a true estimate of the lower end of the range of expected toxicity for the notified substance. A conservative estimate of the LD50 for the notified substance as > 2,000 mg/kg can be based on the surrogate data as summarized.

Acute inhalation toxicity

Considering the very low vapor pressure of the notified substance measured as <5 Pa @ 20 ^{o}C, it is expected that its acute inhalation toxicity value would not fall within a range to be of practical concern. This expectation is reinforced with test results showing the lack of deaths following exposure to a saturated atmosphere of the surrogate 4 substance. Thus, there is a lack of acute inhalation hazard concern anticipated for the notified substance.

Acute dermal toxicity

Acute dermal toxicity study results are available for surrogates 4 and 5. The lower LD50 value of > 2,000 mg/kg for surrogate 5 which itself suggests a low acute dermal toxicity potential. However, the LD50 value of >10,000 mg/kg for surrogate 4 suggests the notified substance may even fall within a range that could be regarded as being practically nontoxic. It is certainly reasonable and conservative to estimate that the acute dermal LD50 value of the notified substance would fall within the range of > 2000 mg/kg.

Skin irritation

Surrogates 1, 4 and 5 were all found to be not irritating to the skin of test animals. These data provide a reasonable basis for concluding that the notified substance can be regarded as not being a skin irritant.

Skin sensitization

The demonstrated lack of skin sensitization responses observed in studies of surrogate substances 5 and 6, which together are composed of the types of components like those found in the notified substance, suggest it is not a sensitizer.

Repeated dose toxicity

Surrogate 2- Docosanol, representative of long chain normal alcohols contribution

A 26 week repeat dose oral toxicity was conducted on docosanol in rats. Doses were 10, 100 and 1000mg/kg bw/day (nominal) in 1% aqueous Tween 80. The test method was equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents).
Result: NOAEL: 1000 mg/kg bw/day (nominal) (male/female) based on: (test mat.) No adverse effects observed.

A 26 week repeat dose oral toxicity of docosanol was also conducted on Beagle dogs. Doses were 20, 200 and 2000mg/kg bw/day (nominal) in 1% aqueous Tween 80. Result: NOAEL: 2000 mg/kg bw/day (nominal) (male/female) based on: (test mat.) No adverse effects observed.

These two studies show that docosanol is of low toxic potency following repeated oral administration in two different species. It is reasonable to take these results as being representative of the anticipated low toxic potency of the structurally similar group of long chain alcohols that compose > 80% of the notified substance. Also, given their presence at such high concentration, it is reasonable to expect that they would exert the overwhelming contribution to the overall anticipated repeated dose toxicity potency of the notified substance. As such, it is reasonable to conclude that based on these results alone, the notified substance would itself be expected to have a low repeat dose toxicity potency potential.

Surrogate 3- Ethene, homopolymer, oxidized, hydrolyzed, distn. residues, from C16-18 alcs. manuf., representative of non-normal long chain alcohol contribution

Surrogate substance 3 was tested in a 90-day repeated dose toxicity study in which Wistar rats were dosed at levels of 100, 300, and 1000 mg/kg body weight day. No test item-related mortality was observed, and no toxicological effects were found in clinical observations, functional observations, body weight development, food consumption, hormone analysis, hematology and coagulation, clinical biochemistry, urinalysis, gross macroscopic findings at necropsy and organ weights in all treated dose groups. At the histopathology evaluation no test item-related changes were observed. The no observed adverse effect level (NOAEL) is 1000 mg/kg body weight/day. (ref. 34)

There is considerable overlap in the composition of surrogate substance 3 with that of the notified substance. This is expected since that both substances are residual products produced as the products of a distillation step. Because of similarity in the production progress used in their manufacture, the same types of compositionally predominate linear alcohol components found in the notified substance are also present in this surrogate substance but in addition to this the types components found in residue products are also present. Consequently, the results of this study which demonstrate the low potency of repeated dose toxicity of this surrogate substance present a realistic and compositionally holistic picture for the anticipated repeat dose toxicological capacity of the notified substance. As such, it is reasonable to conclude that the notified substance would be of low repeat dose toxicological potential and not of practical concern.

Surrogate 5- Behenyl Bottoms, Alcohols, C18-22, distn. Residues, 1160164-88-4

The surrogate 5 substance was administered in 1% Carboxymethylcellulose and 0.2% TWEEN® 80 in water as the vehicle. Exposure was for 90 days (once daily) according to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents). Results: NOEL: 1000 mg/kg bw/day (actual dose received) (male/female) based on: clinical signs.

As mentioned earlier, the composition of this surrogate is distinctive as it contains even lower amounts of the normal long chain alcohols of the type found in the notified substance, but significantly higher levels of the other classes of components, besides the normal alcohols, that are present at lower concentrations than those found in the notified substance or even in the surrogate 4 substance. The inclusion of this data allows the characterization of the contribution of these distinctive components to the repeated dose toxicological properties of the notified substance.

Since this surrogate substance exhibited a low degree of potency for repeated dose toxicity, which even further support the conclusion that it is reasonable expect that the presence of components other than the normal alcohols in the notified substance would not be expected to have an adverse impact on the overall expected repeated dose potency of the notified substance.

Overall conclusion for the expected repeat dose toxicity capacity for the notified substance

Collectively, these results of these studies suggest that a low repeat dose toxicity potency can be anticipated for the notified substance. The representative results of the study on docosanol provides convincing support the idea that the long chain linear alcohols of the type found in the notified substance are of sufficiently low toxic potency to be regarded as practically nontoxic. The results of studies of these two residue products are supportive of the expectation that the other types of substances found in the notified substances besides the long chain alcohols of the docosanol-like type, are not expected to exert an adverse impact on toxicity as exhibited by the lack of adverse impact on toxicity even though present at higher levels than that found in the notified substance.

Genetic toxicity

In vitro gene mutation (e.g. Ames test)

The results of in vitro gene mutation study on the long chain linear alcohol, docosanol (surrogate 2) demonstrates the absence of a mutagenic response in vitro. As was the case for surrogate, the results of in vitro gene mutation studies on surrogate substances 3 and 5, also demonstrate the absence of a mutagenic response in vitro.

Collectively, these results of these studies suggest that a low repeat dose toxicity potency can be anticipated for the notified substance. The representative results of the study on docosanol provides convincing support the idea that the long chain linear alcohols of the type found in the notified substance are of sufficiently low toxic potency to be regarded as practically nontoxic. The results of studies of these two residue products are supportive of the expectation that the other types of substances found in the notified substances besides the long chain alcohols of the docosanol-like type, are not expected to exert an adverse impact on toxicity as exhibited by the lack of adverse impact on toxicity even though present at higher levels than that found in the notified substance.

In vitro mammalian chromosomal aberrations

In vitro mammalian chromosomal aberration study on the long chain linear alcohol, Docosanol (surrogate 2), resulted in the absence of a response. This result is consistent with the results obtained on surrogate substances 3 and 5, which also demonstrated the absence of a chromosomal aberration response in vitro.

Collectively, these results of these studies suggest that a lack of capacity to elicit a chromosomal aberration response can be anticipated for the notified substance. The representative results of the study on docosanol and Eicosanol provides convincing support the idea that the long chain linear alcohols of the type found in the notified substance are of sufficiently low toxic potency to be regarded as practically nontoxic. The results of studies of these two residue products provide convincing support of the expectation that the other types of substances found in the

notified substances besides the long chain alcohols of the docosanol-like type, are not expected to exert an adverse impact on toxicity as exhibited by the lack of adverse impact on toxicity even though present at higher levels than that found in the notified substance.

In vitro mammalian mutagenicity

An In vitro mammalian mutagenicity assay conducted on the long chain linear alcohol, docosanol (surrogate 2), resulted in the absence of a response. This result is consistent with the results obtained on surrogate substances 3 and 5, which also demonstrated the absence of the capacity to elicit a response in the same assay.

The information summarized above suggest that a lack of capacity to elicit a mammalian mutagenicity response in vitro can be anticipated for the notified substance. The representative result on Eicosanol provides convincing support for the idea that the long chain linear alcohols of the type found in the notified substance would also lack this same capacity. The conclusion is complimented by the results of studies of these two residue products provide convincing support of the expectation that the other types of substances found in the notified substances besides the long chain alcohols of the docosanol-like type, are not expected to exert an adverse influence on this capacity and that a lack of in vitro mammalian mutagenetic activity as would be evidenced in this assay is expected for the notified substance.

In vivo mammalian chromosomal aberrations or gene mutation

The results of an In vivo mammalian mutagenicity test for Docosanol (surrogate 2) demonstrate an absence of capacity to induce a mutagenic response in mammalian cells in vivo.

It is reasonable to take this result as being representative of the anticipated response for this endpoint for the structurally similar group of long chain alcohols that compose > 80% of the notified substance. Given their presence at such high concentration, it is reasonable to expect that these alcohols would exerted the overwhelming contribution to the anticipated capacity of the notified substance in this regard. As such, it is reasonable to conclude that based on this result alone, the notified substance would itself be expected to lack the capacity to elicit a response for In vivo mammalian mutagenicity as indicated by this assay.

Overall Summary

The case has been made that there are significant similarities between the composition of the various surrogate substances and the notified substance. It has also been shown that there is reason to believe that the linear long chain alcohols that are the predominant (> 80%) species substances found in the notified substance are of themselves of low acute and repeat dose toxicity potency. Furthermore, it has been shown

that for this class of substance it is reasonable to conclude that they also lack the capacity to cause irritation, sensitization or genotoxic responses as indicated by the type of assays summarized. This would be enough evidence in and of itself to conclude that the notified substance can be regarded as of the same character and may be considered nonhazardous. However, this information has also been further complimented by information that shows that the other types of substances besides these alcohols which are found at lower concentrations in the notified substance can also be considered nonhazardous and without capacity to produce any significant influence of an adverse nature to the overall toxicological character of the notified substance. The strength of evidence obviates the need for any further testing in order to adequately assess the toxicological capacity of the notified substance without further sacrifice of animals to meet the purposes of this NSN review.