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The Flavor and Fragrance High Production Volume Consortia

The Terpene Consortium

Revised Robust Summaries for Ionone Derivatives

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Methyl ionone (mixture of isomers)

CAS No. 1335-46-2

alpha-iso-Methylionone

CAS No. 127-51-5

FFHPVC Terpene Consortium Registration Number

**Submitted to the EPA under the HPV Challenge Program by:
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Table of Contents

1	CHEMICAL AND PHYSICAL PROPERTIES	1
1.1	MELTING POINT	1
1.2	BOILING POINT	3
1.3	VAPOR PRESSURE	4
1.4	N-OCTANOL/WATER PARTITION COEFFICIENT	6
1.5	WATER SOLUBILITY.....	8
2	ENVIRONMENTAL FATE AND PATHWAYS.....	10
2.1	PHOTODEGRADATION	10
2.2	STABILITY IN WATER.....	11
2.3	BIODEGRADATION	12
2.4	FUGACITY	16
3	ECOTOXICITY.....	31
3.1	ACUTE TOXICITY TO FISH.....	31
3.2	ACUTE TOXICITY TO AQUATIC INVERTEBRATES.....	34
3.3	ACUTE TOXICITY TO AQUATIC PLANTS	36
4	HUMAN HEALTH TOXICITY.....	39
4.1	ACUTE TOXICITY	39
4.2	GENETIC TOXICITY	46
4.2.1	<i>In vitro Genotoxicity</i>	46
4.2.2	<i>In vivo Genotoxicity</i>	52
4.3	REPEAT DOSE TOXICITY.....	53
4.4	REPRODUCTIVE TOXICITY.....	61
4.5	DEVELOPMENTAL/TERATOGENICITY TOXICITY	62

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The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al.*, 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 Chemical and Physical Properties

1.1 Melting Point

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for substance	Calculated
Method/guideline	Mean or Weighted
Melting Point	45.26 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency
Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for substance	Calculated
Method/guideline	Mean or Weighted

Melting Point 59.38°C
Data Qualities Reliabilities Reliability code 4. Not assignable.
Remarks for Data Reliability Code 4. Calculated.
References MPBPWIN EPI Suite (2000) US Environmental Protection Agency

Substance Name *alpha*-Methylionone

CAS No. 127-42-4

Remarks for substance Calculated

Method/guideline Mean or Weighted

Melting Point 53.53°C

Data Qualities Reliabilities Reliability code 4. Not assignable.

Remarks for Data Reliability Code 4. Calculated.

References MPBPWIN EPI Suite (2000) US Environmental Protection Agency

Substance Name *beta*-Methylionone

CAS No. 127-423-5

Remarks for substance Calculated

Method/guideline Mean or Weighted

Melting Point 62.86°C

Data Qualities Reliabilities Reliability code 4. Not assignable.

Remarks for Data Reliability Code 4. Calculated.

References MPBPWIN EPI Suite (2000) US Environmental Protection Agency

1.2 Boiling Point

Substance Name	Methyl ionone (mixture of <i>isomers</i>)
CAS No.	1335-46-2
Method/guideline	Measured
Boiling Point	266.2 °C
Pressure	1013 mb
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Hoffmann-LaRoche, Inc. (2000) Isoraldeine 70 Safety Data Sheet. Red Corner Report, No. B-108,080 vom 17.6., 1983, Kradolfer (Nr. 95931). Unpublished report.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Measured
Boiling Point	238 C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction..
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	Methyl ionone (mixture of <i>isomers</i>)
CAS No.	1335-46-2
Method/guideline	Measured
Boiling Point	238 C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	<i>alpha-iso</i> -Methylionone
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CAS No.	127-51-5
Method/guideline	Calculated /Adapted Stein & Brown method
Boiling Point	271.6 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Calculated /Adapted Stein & Brown method
Boiling Point	274.6 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

1.3 Vapor Pressure

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Measured
Vapor Pressure	0.006 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Measured

Vapor Pressure	0.005 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated/modified Grain method
Vapor Pressure	0.00127 mm Hg
Temperature	25 °C
Remarks for Test Conditions	Experimental boiling point used 266.2 C.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

Substance Name	Methylionone
CAS No.	1335-46-2
Method/guideline	Calculated/modified Grain method
Vapor Pressure	0.0093 mm Hg
Temperature	25 °C
Remarks for Test Conditions	Experimental boiling point used 266.2 C.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

1.4 n-Octanol/Water Partition Coefficient

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	Main isomer, <i>alpha-iso-methylionone</i> , 87.8%
Method/guideline	Measured/OECD No.117; reverse phase high performance liquid chromatographic method
GLP	Yes
Year	1994
Log Pow	4.6
Temperature	24 °C
Remarks for Test Conditions	The test substances and seven substances of log Pow (calibration solution) are subjected to HPLC (HP 1050) with a UV-visible detector at 24 °C. Following calibration, the HPLC of test solutions are chromatographed followed by the calibration solution again. Measured retention times are used to determine log Pow.
Conclusion Remarks	The log Pow of <i>alpha-iso-methylionone</i> is determined to be 4.6 at 24 °C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Rudio J. (1994a) Partition coefficient n-octanol/water of Isoraldeine according to OECD Guideline No. 117. Study No. 94-E70. Unpublished report.

Substance Name	<i>beta-Ionone (97%)</i>
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methylionone (mixture of isomers), <i>beta-ionone</i>
Method/guideline	Measured/OECD No.117; reverse phase high performance liquid chromatographic method
GLP	Yes
Year	1994
Log Pow	4.1
Temperature	24 °C
Remarks for Test Conditions	The test substances and seven substances of log Pow (calibration solution) are subjected to HPLC (HP 1050) with a UV-visible detector at 24 °C. Following calibration, the HPLC of

Conclusion Remarks	test solutions are chromatographed followed by the calibration solution again. Measured retention times are used to determine log Pow. The log Pow of <i>beta</i> -ionone is determined to be 4.1 at 24 °C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Rudio J. (1994b) Partition coefficient n-octanol/water of ionone, <i>beta</i> synt according to OECD Guideline No. 117. Study No. 94-E68. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Measured/OECD No. 117
GLP	Yes
Year	1994
Log Pow	4.6
Temperature	24 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Givaudan-Roure Inc. (1994) Partition Coefficient n-octanol/water of methyl ionone. Unpublished report.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Log Pow	4.84
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U S Environmental Protection Agency

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Calculated

Log Pow	4.84
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U S Environmental Protection Agency

1.5 Water Solubility

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Measured
GLP	Yes
Year	1991
Value (mg/L) at Temperature	16 mg/L at 20 °C
Remarks for Test Conditions	The solubility of the test substances was determined according to the OECD Guidelines for Testing Chemicals No. 105, "Water Solubility" (flask method)
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Schlienger C. (1992b) 96-Hour acute toxicity study with Isoraldein 70 in rainbow trout. Report No. B-161751. Unpublished report.

Substance Name	Methylionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Measured for <i>gamma</i> methyl ionone (one of three methylionone isomers)
Value (mg/L) at Temperature	0.009 % W/V (90 mg/L) at 25 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Bush, Boake, Allen, Inc. (BBA) (1990) Biodegradability of p-t-butyl- <i>alpha</i> -methylhydrocinnamic aldehyde and methyl- <i>alpha</i> -ionone. Unpublished report.

Substance Name	<i>alpha-iso</i> -Methylionone
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CAS No.	127-51-5
Method/guideline	Calculated
Value (mg/L) at Temperature	4.8 mg/L at 25 °C
Remarks for Test Conditions	Log Kow used: 4.6 (measured)
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN 2000 US Environmental Protection Agency

2 Environmental Fate and Pathways

2.1 Photodegradation

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Test Type	AOPWIN
Half-life t_{1/2}	0.752 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency
Substance Name	<i>alpha-n-Methylionone</i>
CAS No.	127-42-4
Method/guideline	Calculated
Test Type	AOPWIN
Half-life t_{1/2}	0.849 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency
Substance Name	<i>beta-n-Methylionone</i>
CAS No.	127-43-5
Method/guideline	Calculated
Test Type	AOPWIN
Half-life t_{1/2}	0.536 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References

AOPWIN EPI Suite (2000) US Environmental Protection Agency

2.2 Stability in Water

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method	Bond SAR method
Test Type	Calculated
Remarks Results	Half-life: river 8 .655 hours; lake 168.9 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency

2.3 Biodegradation

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	Mixture of 55% <i>alpha-iso-methylionone</i> and 28% <i>alpha-methylionone</i>
Method	Sealed vessel test (based on OECD 301B)
Test Type	CO2 production test
GLP	No
Year	1992
Contact Time	56 days
Innoculum	Unacclimatized activated sludge
Remarks for Test Conditions	The test material (10 mg DOC/L) and secondary effluent from an unacclimatized activated sludge were shaken in a sealed vessel at 14-22 °C for 56 days. The headspace carbon dioxide level and inorganic carbon in the test medium was analyzed.
Degradation % After Time	61.8% after 28 days
10 day Window Criteria	No
Total degradation	60% pass level after 28 days
Remarks Results	Test intended to monitor inherent and ultimate biodegradability using test protocol (301B) used to measure ready biodegradability in 28 days. Test suitable for analysis of volatile substances
Conclusion Remarks	The test substance was considered as inherently biodegradable under modified ready test conditions.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	King J. M. (1992) The inherent biodegradability of base perfumes in the sealed vessel test. BD/PER/15. Unpublished report.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	Mixture of isomers composed of 60-70% <i>alpha iso-methylionone</i> , 17-30% <i>beta-iso-methylionone</i> , <i>alpha-</i> and <i>beta-methylionone</i> , 91.4% pure: Isoraldein 70
Method/guideline	Modified MITI Test (II)/OECD 302C

Test Type	Inherent Biodegradability: Modified MITI Test (II), 5/1981
GLP	Yes
Year	1992
Contact Time	28 days
Innoculum	Mixture (1:1) from city sewage plant and chemical sewage plant
Remarks for Test Conditions	The test substance (30 mg/L) or reference substances (100 mg/L) sodium benzoate was inoculated with a mixture of activated sludge (100 mg dry sludge/L) in a closed oxygen consumption measuring device for 28 days at 25 °C. Oxygen concentration was monitored continuously using a BOD meter. Percent biodegradation values were arithmetic mean of 2 or 3 independent measurements.
Degradation % After Time	63.4% after 56 days
Results	Negative degradation values were recorded from days 1 to 7 for the test substances. Maximum degradation rate was 3.5%/day at days 9-12 and was reduced to 0.9% at day 19. The reference substance was 100% degraded after 28 days.
10 day Window Criteria	No
Time Required for 10% Degradation	12 days
Classification	Isoraldeine gave evidence of inherent, primary biodegradation and was slightly toxic to microorganisms
Conclusion Remarks	A mixture of methylionones containing 60-70% <i>alpha</i> -isomethylionone shows evidence of inherent, primary biodegradability in an MITI II Test. It was slightly toxic for activated sludge microorganisms.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Schlienger C. (1992a) Inherent biodegradability: Modified MITI-TEST (II) for Isoraldein 70. GLP Test No. PSU 92/2-MII. Unpublished Report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Mixture of isomers composed of 55-65% <i>alpha</i> isomethylionone, 22-32% <i>alpha</i> -methylionone, 1-5% <i>beta</i> -methylionone, and 4-8% <i>beta</i> -isomethylionone, 1-5% of <i>beta</i> or <i>gamma</i> -methylionone, 98%, sum of isomers
Method/guideline	Biodegradability test
Test Type	Method F, Assessment of biodegradability, 1981
GLP	No
Year	1990

Contact Time	31 days
Innoculum	Buffered solution of activated sludge
Remarks for Test Conditions	Methylionone mixture was mixed with a buffered solution of 30 mg activated sludge/L. The concentration of the test material was calculated to be 50 mg DOC/L. The solution was stirred under fully aerobic conditions in the dark at 20 °C for 28 days. A hard standard of orthophenyldiamine (51 mg DOC/L) was run at the same time
Degradation % After Time	99.1% at day 31
Results	The test material was 95.7% degraded at day 1 and 99.1% at day 31. The hard standard was 12% biodegraded after 14 days
Time required for 10% degradation	Less than 1 day
Total degradation	Yes
Classification	Completely biodegradable
10 day window criteria	Yes
Conclusion Remarks	The mixture of methylionone isomers was completely biodegradable within 28 days
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
Reference	Stickley D. P. (1990) Biodegradability of Lilestrialis and gamma-methylionone 600 UC. Report No. 8720. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Mixture of isomers composed of 60-70% <i>alpha iso</i> -methylionone, 17-30% <i>alpha</i> -methylionone, 0-8% <i>beta</i> -methylionone, and 0-8% <i>beta</i> -isomethylionone, 97.6%, sum of isomers
Method/guideline	MITI Test/OECD 301C
Test Type	Ready Biodegradability Test
GLP	Yes
Year	1990
Contact Time	28 days
Innoculum	Mixture of sludge from city sewage plant (Geneva) and chemical sewage plant (Vernier-ouest, Geneva)
Remarks for Test Conditions	Initial test concentrations: activated sludge, 30 mg/L; Test substance, 107 mg/L; Reference substances, aniline, 93 mg/L. Temperature maintained at 20 °C in a closed system oxygen consumption apparatus.
Degradation % After Time	70.5%

Results	Ionone mixture is biodegradable after 28 days
Time required for 10% degradation	5 days
10 day Window Criteria	Yes
Total degradation	70.5%
Classification	60% pass level exceeded after 28 days
Remarks Results	Reference substance achieved maximum biodegradability within 15 days
Conclusion Remarks	Methylionone (mixture of isomers) is readily biodegradable after 28 days
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Calame R. and Ronchi W. (1990) Isoraldeine 70. Determination of ready biodegradability. Report No. 90-42/B. Unpublished report.

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methylionone (mixture of isomers), <i>beta</i> -ionone
Method/guideline	Respirometric method
Test Type	Biodegradability test
GLP	No
Year	1991
Contact Time	28 days
Innoculum	Activated sludge
Remarks for Test Conditions	In a basic culture medium, 100 mg/L of test material or 100 mg/L of reference substance (aniline) and 30 mg/L activated sludge and oxygen concentration was measured at daily intervals over 28 days.
Degradation % After Time	80% after 28 days
10 day window criteria	Yes
Time required for 10% degradation	5 days
Remarks for Results	<i>Beta</i> -Ionone was 80% biodegraded over 28 days and the reference substance was 89% degraded over 28 days
Conclusion Remarks	<i>beta</i> Ionone underwent ready biodegradation over 28 days in a respirometric test
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.

Reference Givaudan-Roure Inc. (1991) Biodegradability test of ionone, *beta*, and synthetic. Report No. 5992503. Unpublished report.

2.4 Fugacity

Substance	<i>alpha-iso</i> -Methylionone
CAS	127-51-5
Model Conditions	25 C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	EQC Fugacity Level III
Input parameters	MW, VP(0.006 mm Hg), log Kow (4.6), water solubility (16 mg/L), estimated MP, 45.3 °C, BP, 266.4 °C
Year	2000
Media	Air-Water-Soil-Sediment Partition Coefficients
Model data and results	Compartment half-lives, hours: Air=0.338; Water=900; Soil=900; Sediment=3600
Estimated Distribution and Media Concentration	Air=0.0307% Water=18.8% Soil=64.7% Sediment=16.5%
Conclusion remarks	Substance is predicted to persist in the environment for 668 hours.
Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
Substance	Methyl ionone (mixture of isomers)
CAS	1335-46-2
Model Conditions	25 C, 1000 lbs.

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	EQC Fugacity Level III
Input parameters	MW (206.33 g/mole), VP(0.005 mm Hg), log Kow (4.91), water solubility (5 mg/L), estimated MP, 59.4 °C, BP, 274 °C
Year	2000
Media	Air-Water-Soil-Sediment Partition Coefficients
Model data and results	Compartment half-lives, hours: Air=0.459; Water=900;Soil=900;Sediment=3600
Estimated Distribution and Media Concentration	Air=0.0475% Water=16.1% Soil=67.4% Sediment=16.5%
Conclusion remarks	Substance is predicted to persist in the environment for 641 hours.
Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Water
Estimated Distribution and Media Concentration	2.49%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.

References

Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Soil
Estimated Distribution and Media Concentration	87.7%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Sediment
Estimated Distribution and Media Concentration	1.95%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.

References Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	1.061%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Fish

Estimated Distribution and Media Concentration	0.0050%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Aerosol
Estimated Distribution and Media Concentration	0.000088%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I

Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Air-Water Partition Coefficient
Absorption coefficient	0.0062
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Soil-Water Partition Coefficient
Absorption coefficient	783
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-580-56-8
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model

Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Sediment-Water Partition Coefficient
Absorption coefficient	1570
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Suspended Sediment-Water Partition Coefficient
Absorption coefficient	4900
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5

Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Fish-Water Partition Coefficient
Absorption coefficient	1990
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Aerosol-Air Partition Coefficient
Absorption coefficient	564000
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Air-Water Partition Coefficient
Absorption coefficient	0.137
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Soil-Water Partition Coefficient
Estimated Distribution and Media Concentration	1390
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental

models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Sediment-Water Partition Coefficient
Absorption coefficient	2790
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Suspended Sediment-Water Partition Coefficient
Absorption coefficient	8710
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or

metabolism.

References

Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Fish-Water Partition Coefficient
Absorption coefficient	3540
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Aerosol-Air Partition Coefficient
Absorption coefficient	559000

Data Qualities Reliabilities Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.

References Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Air
Estimated Distribution and Media Concentration	51.3%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log

Media	Water
Estimated Distribution and Media Concentration	0.747%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Soil
Estimated Distribution and Media Concentration	46.9%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay

Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Sediment
Estimated Distribution and Media Concentration	1.04%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.033%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Fish
Estimated Distribution and Media Concentration	0.0026%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Aerosol
Estimated Distribution and Media Concentration	0.00057%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

3 Ecotoxicity

3.1 Acute Toxicity to Fish

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	Mixture of isomers composed of 60-70% <i>alpha</i> isomethylionone, 17-30% <i>beta-iso-methylionone</i> , <i>alpha</i> - and <i>beta</i> -methylionone, 91.4% pure
Method/guideline	Fish acute toxicity test/OECD 203
Test Type	Experimental
GLP	Yes
Year	1992
Species/Strain/Supplier	Rainbow trout (<i>Oncorhynchus mykiss</i>)
Exposure Period	96 hour
Remarks for Test Conditions	Rainbow Trout (average length, 5.8 cm), acclimatized for 12 days, were exposed to a series of 5 test concentrations of 0, 7.8, 10.9, 15.3, 21.4, or 30 mg/L dispersed in Polysorbate 80 (10 mg/L) for 96 hours at 17.1 °C. Control fish were exposed to Polysorbate 80 (10 mg/L). Fish were observed twice daily for mortality and symptoms. pH values and water temperature were monitored after substance addition at 24 hour intervals. Dissolved oxygen was measured at the beginning of the experiment and at 96 hours.
Observations on precipitation	No precipitation
Nominal concentrations as mg/L	0, 7.8, 10.9, 15.3, 21.4, and 30 mg/L test material in 10 mg/L Polysorbate 80 dispersant.
Remarks fields for results	Mortality at 96 hours: 0/10 at 0 mg/L (10 mg/L Polysorbate 80); 0/10 at 7.8 mg/L (7.8 mg/L Polysorbate 80); 8/10 at 10.9 mg/L (10 mg/L Polysorbate 80); 10/10 at 15.3 mg/L and higher (10 mg/L Polysorbate 80). pH values, 8.0-8.9; dissolved oxygen 9.0-9.7 mg/L; water temperature, 17 °C; hardness, 260-299 mg/L; calcium, 55.9-65.6 mg/L. LD0 = 7.8 mg/L and LD100 = 15.3 mg/L
Conclusion Remarks	LC50 = 10.9 mg/L from linear least square regression line obtained from plot of log concentration versus % mortality data
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Schlienger C. (1992b) 96-Hour acute toxicity study with isoraldein 70 (Ro 01-8915/000) in rainbow trout. Unpublished report.

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>beta</i> -ionone
Method/guideline	Fish acute toxicity test
Test Type	Experimental
GLP	No
Year	1989
Species/Strain/Supplier	Rainbow trout (<i>Oncorhynchus mykiss</i>)
Exposure Period	48 hour
Remarks for Test Conditions	Rainbow Trout (length, 6-8 cm) were exposed to 0, 5, and 10 mg/L <i>beta</i> -ionone for 48 hours at 16+/-1 °C.
Observations on precipitation	Not reported
Nominal concentrations as mg/L	0, 5, or 10 mg/L
Remarks for Results	Mortality at 48 hours: 0/10 at 0 mg/L; 0/10 at 5 mg/L; 10/10 at 10 mg/L
Conclusion Remarks	LC0 = 5 mg/L and LC100 = 10 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods, but results are consistent with current results obtained by current OECD guideline study
Reference	Grothe J. (1989) Ecotoxicity attachment for <i>beta</i> -ionone. Roche report No. E-29/89. Unpublished report.

Substance Name	<i>alpha</i> -iso-Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	14 day
Remarks for Results	Neutral organic SAR
Conclusion Remarks	LC50 = 0.931 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

Reference ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Remarks for Substance	CLOGP
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Conclusion Remarks	Vinyl/allyl ketones: LC50 = 2.04 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency..

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	SRC
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Conclusion Remarks	Vinyl/Allyl ketones: LC50 = 2.88 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour

Conclusion Remarks	Vinyl/allyl ketones: LC50 = 0.296 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Mixture of isomers composed of 55-65% <i>alpha</i> isomethylionone, 22-32% <i>alpha</i> -methylionone, 1-5% <i>beta</i> -methylionone, and 4-8% <i>beta</i> -isomethylionone, 1-5% of <i>beta</i> or <i>gamma</i> -methylionone, 98%, sum of isomers
Method/guideline	OECD 202
Test Type	Experimental
GLP	Yes
Year	2003
Analytical procedures	HPLC/UV detector
Species/Strain	Daphnia magna/Aquatic Biosystems, Inc.
Test details	48 hrs.
Remarks for Test Conditions	Juvenile daphnids (<24 hours old) produced from an in-house culture of adults were maintained at the contract laboratory under test conditions for 45 days. During the 48 hours prior to testing, the daphnid culture was maintained in 100% dilution water under static, renewal conditions for 48 hours. There was no mortality during the 48 hours prior to test and the test organisms appeared free of disease, injuries, or abnormalities. The daphnid culture produced young before day 12 and a subsample of adults produced on average, more than 3 young per day during the 7 days prior to the beginning of the test. The test substance was provided via an intermittent flow proportional diluter. Ten daphnid were randomly selected for each replicate test. Tests were performed at 5 nominal concentrations. During the 48-hr test, daphnid were exposed to 16 hours of light and 8 hours of darkness. Mortality, immobility, and sub-lethal effects were determined visually at 0, 24, and 48 hours. Test temperature was maintained at 20.0-20.7 °C
Nominal concentrations as mg/L	0.78, 1.3, 2.2, 3.6, and 6.0 mg/L
Measured concentrations as mg/L	0.621, 1.14, 1.82, 2.99, and 5.32 (mean conc)

Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hr EC50=2.65 mg/L and 48 hr LC50=3.11 mg/L; NOEC 1.14 mg/L
Biological observations	The number of surviving daphnids at 48 hours for duplicate runs at each mean measured concentration was: 0 mg/L, 10/10; 0.621 mg/L, 9/10 & 10/10; 1.14 mg/L, 9/10 10/10; 1.82 mg/L, 8/10 & 9/10; 2.99 mg/L, 7/10 & 4/10; 5.32 mg/L 0/10 & 0/10.
Control response satisfactory?	yes
Appropriate statistical evaluations?	Probit method (Stephan, 1978)
Remarks fields for results	The measured concentrations after 24 and 48 hours were 80-89% of the nominal concentrations, with the concentration being held steady throughout the test period. The respective ranges for conductivity, pH, dissolved oxygen, and temperature were: 490-620 umhos/cm, 7.3-7.7, 8.4-9.1 mg/L, and 20.0-20.8C, respectively.
Conclusion remarks	The acute 48-hour EC50 and LC50 for methylionone in Daphnid magna under semi-static conditions were 2.65 and 3.11 mg/L, respectively. The NOEC for methylionone in Daphnid magna is 1.14 mg/L
Reliabilities	Reliability Code No. 1. Reliable without restriction.
Remarks for Data Reliability	The data are obtained by a recognized guideline method and are consistent with chemical structure.
References	Ward T. (2003a) Acute toxicity test with methylionone and the Daphnid, <i>Daphnia magna</i> . Study No. 2469-FF. Private communication to FFHPVC. Unpublished Report.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	<i>Daphnia magna</i>
Remarks for Test Conditions	CLOGP
Exposure period	48 hours
EC50, EL50, LC0, at 24,48 hours	Vinyl/allyl ketones: LC50 = 0.597 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.
Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5

Method/guideline	Calculated
Species/Strain/Supplier	<i>Daphnia magna</i>
Remarks for Test Conditions	SRC
Exposure period	48 hours
EC50, EL50, LC0, at 24,48 hours	Vinyl/allyl ketones: LC50 = 0.672 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.3 Acute Toxicity to Aquatic Plants

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Mixture of isomers composed of 55-65% <i>alpha</i> isomethylionone, 22-32% <i>alpha</i> -methylionone, 1-5% <i>beta</i> -methylionone, and 4-8% <i>beta</i> -isomethylionone, 1-5% of <i>beta</i> or <i>gamma</i> -methylionone, 98%, sum of isomers
Method/guideline	OECD 201 Guideline
Test Type	Experimental
GLP	Yes
Year	2003
Species/Strain/Supplier	Green algae/Selenastrum capricornutum/UTEX 1648
Exposure period (duration)	72 hrs
Analytical monitoring	HPLC/UV detector
Remarks for Test Conditions	Green Algae/Selenastrum capricornutum/U. of Texas was maintained at test conditions for 14 days prior to the test. The culture was growing in at least 2 subcultures prior to the initiation of the test. In a range finding test, the number of cells/mL was >100 % of controls at 0.01 , 0.10, and 1.0 mg/L, 21% at 10 mg/L, and <3% at 100 mg/L after three days. In the definitive test, algae was treated with nominal concentrations of 0, 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/L for 72 hours. pH was adjusted to 7.5 and solutions were exposed for 24 hours of light of intensity, 400-410 foot candles. The number of algal cells/mL as well as relative size, cell shapes, color, adherence and aggregation of cells was determined. At 24, 48, and 72 hours 3 treatment and 6 control vessels were sacrificed to determine

	the number of algal cells/mL. Concentrations were determined by HPLC.
Nominal concentrations as mg/L	0, 0.5, 1.0, 2.0, 4.0, 8.0, and 16 mg/L
Measured concentrations as mg/L	Initial mean measured concentrations 0.404, 0.954, 1.68, 2.94, 6.74, and 14.0 mg/L; Final measured were 40-54% of nominal concentrations
Unit	mg/L
NOEC, LOEC or NOEL, LOEL	72 hr EC50=7.47 mg/L based on average specific growth rate; 72-hr EC50=3.23 mg/L calculated using the number of cells/mL; 72-hr EC50= 2.89 mg/L using the area under the growth curve. The 72-hr NOEC=1.68 mg/L
Biological observations	Control algal populations grew at an acceptable rate (464,000 cells/ml) after 72 hours. Incubation temperatures were in the range from 23.9 to 24.2 C over the 72 hours and pH was unchanged by the test substance. At the conclusion of the test, samples of test media from each test vessel with maximal growth inhibition were combined with fresh media. After 48 hours incubation the number of cells increased from 3200 cells/mL to 322,000 cells/mL at 2.94 mg/L suggesting that the toxic effects were algistatic.
Appropriate statistical evaluations?	EC50 values determined by weighted least squares non-linear regression (Bruce and Versteeg, 1992); NOEC was determined using a one-way analysis of variance (ANOVA) and Bonferroni's test (Gulley et al. 1990)
Conclusion remarks	The acute toxicity of methylionone measured as a 50% decrease in growth and reproduction of freshwater algae was estimated to be 72 hr EC50=7.47 mg/L based on average specific growth rate; 72-hr EC50=3.23 mg/L calculated using the number of cells/mL; 72-hr EC50= 2.89 mg/L using the area under the growth curve. The 72-hr NOEC=1.68 mg/L
Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	OECD 201 Guideline study
References	Ward T. (2003b) The growth and reproduction toxicity test with heptanal and freshwater alga, <i>Selenastrum capricornutum</i> . OECD 201. Study No. 2468-FF. Private Communication to FFHPVC. Unpublished Report.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Remarks for Substance	CLOGP
Conclusion Remarks	Vinyl/allyl ketones: EC50 = 0.266 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.

Remarks for Data Reliability Code 4. Calculated.
Reference ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Remarks for Substance	SRC
Conclusion Remarks	Vinyl/allyl ketones: EC50 = 0.332 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

4 Human Health Toxicity

4.1 Acute Toxicity

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1967
Species/strain	Mouse/CF-1
Sex	Male and Female
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	CF-1 mice of both sexes were orally administered the compound. LD50 was calculated by the method of Miller and Tainter (Proc. Soc. Exptl. Biol. Med. 57:261, 1944)
Value LD50 or LC50 with confidence limits	LD50 = 8714 (95% C.I., +/- 252 mg/kg)
Number of deaths at each dose level	
Remarks for Results	
Conclusion Remarks	The oral LD50 was calculated to be LD50 = 8714 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffmann-LaRoche, Inc. (1967) Acute toxicity, eye and skin irritation test on aromatic compounds. Unpublished report.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Not given
Test Type	Acute oral toxicity

GLP	Ambiguous
Year	1973
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The oral LD50 of <i>alpha-iso-methylionone</i> was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1973a) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	<i>alpha-iso-methylionone</i> (pseudo product)
Method/guideline	Not given
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Dose tested: 5900 mg/kg
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	1/10 at 5000 mg/kg

Conclusion Remarks	The oral LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1977b) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	<i>alpha</i> -Ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1967
Species/strain	Mouse/CF-1
Sex	Male and Female
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	CF-1 mice of both sexes were orally administered the compound. LD50 was calculated by the method of Miller and Tainter. (Proc. Soc. Exptl. Biol. Med. 57:261, 1944)
Value LD50 or LC50 with confidence limits	LD50 = 6657 mg/kg (95% C.I., +/- 652 mg/kg)
Conclusion Remarks	The oral LD50 was calculated to be 6650 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffmann-LaRoche, Inc. (1967) Acute toxicity, eye and skin irritation test on aromatic compounds. Unpublished report.

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methylionone (mixture of isomers), <i>beta</i> -ionone
Method/guideline	Litchfield and Wilcoxon, 1949

Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1967
Species/strain	Mouse/CFW
Sex	Male
# of animals per sex per dose	5
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Male CFW-mice were orally administered the compound. Five mice were used per dose level and were observed 72 hours for mortality. LD50 was calculated by the Method of Miller and Tainter (Proc. Soc. Exptl. Biol. Med. 57:261, 1944.
Value LD50 or LC50 with confidence limits	LD50 = 5331 mg/kg (95% C.I., +/- 755 mg/kg)
Conclusion Remarks	The oral LD50 was calculated to be 5331 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffmann-LaRoche, Inc. (1967) Acute toxicity, eye and skin irritation test on aromatic compounds. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl Ionone (Gamma type)
Method/guideline	Not given
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1973
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Observations for mortality and/or systemic effects were made over a 14-day period. 5000 mg/kg of test substance was

	administered to the animals.
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The oral LD50 was shown to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Data Reliabilities Remarks	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1973b) Acute toxicity studies on rats and rabbits. Unpublished Report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl ionone (mixture of isomers: methyl- <i>alpha</i> ionone, <i>alpha</i> - <i>iso</i> -ionone, methyl- <i>beta</i> -ionone, pseudo product)
Method/guideline	Not given
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Dose tested: 5000 mg/kg.
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The oral LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1977a) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.
Substance Name	Methyl ionone (mixture of isomers)

CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>beta</i> -lonone
Method/guideline	Not given
Test Type	Acute intraperitoneal toxicity
GLP	Ambiguous
Year	1965
Species/strain	Mouse
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Intraperitoneal
Vehicle	None
Value LD50 or LC50 with confidence limits	LD50 = 2277 mg/kg
Conclusion Remarks	The intraperitoneal LD50 was calculated to be 2277 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Sporn A., Schobeschm O., Marin, V., Pansitescu, E. and Runcan, L. (1965) The Toxicity of Butyl Acetate, Methyl Naphtyl Ketone and Ionone. <i>Igiena</i> , XII(5), 437-446.

Substance Name	<i>alpha</i> -iso-Methylionone
CAS No.	127-51-5
Remarks for Substance	<i>alpha</i> -iso-methylionone (contains open-chain pseudo product)
Method/guideline	Not given
Test Type	Acute dermal toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Dermal

Remarks for Test Conditions	Doses tested: 2500 and 5000 mg/kg.
Value LD50 or LC50 with confidence limits	Dermal LD50 greater than 5000 mg/kg
Number of deaths at each dose level	6/10 at 5000 mg/kg
Remarks for results	Diarrhea in 2, anorexia and lethargy in 1 at 5000 mg/kg, moderate to severe redness in 4 animals and severe edema in rabbits treated with 2500 mg/kg; severe redness and moderate edema in rabbits treated with 5000 mg/kg.
Conclusion Remarks	The dermal LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1977b) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl ionone (mixture of isomers: methyl- <i>alpha</i> ionone, <i>alpha</i> - <i>iso</i> -ionone, methyl- <i>beta</i> -ionone, pseudo product)
Method/guideline	Not given
Test Type	Acute dermal toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Dermal
Remarks for Test Conditions	Dose tested: 5000 mg/kg
Value LD50 or LC50 with confidence limits	Dermal LD50 > 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Remarks for results	Slight lethargy, ataxia, discharge from nose & mouth, negative righting reflex in 1; severe skin irritation in all animals with moderate to severe edema.
Conclusion Remarks	The dermal LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.

Data Reliabilities Remarks Code 2. Basic data given: comparable to guidelines/standards.

References Moreno O. M. (1977a) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl Ionone (Gamma type)
Method/guideline	Not given
Test Type	Acute dermal toxicity
GLP	Ambiguous
Year	1973
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	8
Vehicle	None
Route of Administration	Dermal
Remarks for Test Conditions	5000 mg/kg of the test substance was applied to abraded rabbit skin.
Value LD50 or LC50 with confidence limits	Dermal LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The dermal LD50 was shown to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1973b) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

4.2 Genetic Toxicity

4.2.1 In vitro Genotoxicity

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Ames

Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1983
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	Up to 3600 ug/plate
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Remarks for Test Conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo(a)pyrene.
Results	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. <i>Fd. Chem. Toxic.</i> 21(6), 707-719.

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>beta</i> -ionone
Method/guideline	Ames
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1986
Species/Strain	<i>Salmonella typhimurium</i> TA 100, TA98, TA97, TA1535, and TA1537
Metabolic Activation	Male Sprague Dawley rat liver microsome fraction S9 from Aroclor induced rats.

Doses/Concentration	1-180 ug per plate
Statistical Methods	Not given
Remarks for Test Conditions	After 48-hour incubation at 37 C, each assay plate was counted. Routine positive control plates were prepared: sodium azide for TA1535 and TA100, 4-nitro-o-phenylenediamine for TA98, and 9-aminoacridine for TA97 and TA1537, 2-aminoanthracen.
Results	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Mortelmans K., Haworth, S., Lawlor, T., Speck, W., Tainer, B and Zeiger, E. (1986) Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. Environmental Mutagenesis, 8(Supp. 7), 1-119.

Substance Name	<i>delta</i> -Ionone
CAS No.	7748-98-7
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>delta</i> -ionone
Method/guideline	Ames
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1983
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	Up to 3600 ug/plate
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Remarks for Test Conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo(a)pyrene
Results	No mutagenic effects

Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. <i>Fd. Chem. Toxic.</i> 21(6), 707-719.

Substance Name	<i>alpha</i> -Ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone
Method/guideline	Ames
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1982
Species/Strain	<i>Salmonella typhimurium</i> TA98 or TA100
Metabolic Activation	With and without rat liver microsome fraction S9
Remarks for Test Conditions	Negative
Results	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Kasamaki A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T. and Urasawa, S. (1982) Genotoxicity of Flavoring Agents. <i>Mutation Research</i> , 105, 387-392.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Ames (plate incorporation method)
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	Yes
Year	1999
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	Up to 5000 ug/plate
Remarks for Test Conditions	A preliminary toxicity study was performed in the first phase and a mutagenicity assay in the second phase. Test article was dissolved in DMSO and tested at up to 5000 ug/plate. No precipitate was observed up to 5000 ug/plate.
Results	In mutagenicity study, no evidence of mutagenicity or precipitation at concentrations up to and including 5000 ug/plate.
Cytotoxic concentration	Toxicity observed with TA 100 at 667 ug/plate with and 5000 ug/plate without S9 activation. In TA 1535 and TA1537, toxicity observed up to 1000 ug/plate with and up to 3333 ug/plate without metabolic activation.
Genotoxic Effects	No evidence of genotoxicity
Appropriate statistical evaluations?	None given
Remarks for results	In mutagenicity study, no evidence of mutagenicity. Toxicity was observed at concentrations of 1800 ug/plate with TA100 and 1800 ug/plate with TA1537.
Conclusion Remarks	No evidence of mutagenicity at concentrations up to and including 5000 ug/plate.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Wagner V.O. III and Caruthers S.M. (1999) Bacterial Reverse Mutation assay of Methyl Ionone. Unpublished report to RIFM.

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>beta</i> -ionone
Method/guideline	Ames

Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	3 umole/plate (600 ug/plate)
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Results	No mutagenicity at 3 umole/plate or 600 ug/plate.
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Remarks for results	No evidence of precipitation or mutagenicity at 600 ug/plate
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Florin I., Rutberg, L., Curvall, M., and Enzell, C. R. (1980) Screening of Tobacco Smoke Constituents for Mutagenicity Using the Ames' Test. Toxicology, 18, 219-232.

Substance Name	<i>alpha</i> -Ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone
Method/guideline	Chromosomal aberration
Test Type	Chromosomal aberration
System of Testing	Chinese hamster ovary cells
GLP	No
Year	1982
Species/Strain	Chinese hamster
Doses/Concentration	25 mMolar (5150 mg/L or 5150 ug/mL)
Remarks for test conditions	At 25 millimolar (5150 ug/mL), significant increases in chromosome aberrations were found.
Results	Cytogenetic effects at 25 mM

Cytotoxic concentration	Not given
Genotoxic Effects	Increase in chromosomal aberrations
Appropriate statistical evaluations?	None given
Conclusion remarks	Inconclusive results.
Remarks for results	No attempt to monitor cytotoxicity in CHO cells. Limited data presented in article.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T. and Urasawa, S. (1982) Genotoxicity of Flavoring Agents. Mutation Research, 105, 387-392.

4.2.2 In vivo Genotoxicity

Substance Name	<i>alpha</i> -Ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler et al., 1977)
Test Type	Sex-linked lethal test
GLP	Ambiguous
Year	1983
Species/Strain	<i>Drosophila melanogaster</i>
Sex	Not reported
Route of Administration	Oral-Diet
Doses/Concentration	20mM
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for Results	Methylionone did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion Remarks	Methylionone did not induce sex-linked recessive lethals in <i>Drosophila melanogaster</i> .
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.

References Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basic and micronucleus tests. *Fd. Chem. Toxicol.*, 21(6), 707-719.

Substance Name	<i>alpha</i> -Ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone
Method/guideline	Micronucleus test (Schmid, 1976)
Test Type	Clastogenic assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	825, 1444, or 2063 mg/kg
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 825, 1444, or 2063 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976). Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970). The mean number of micronucleated PE/1000 PE at 0, 825, 1444, or 2063 mg/kg bw was 1.7, 1.0, 0.7, or 1.9 respectively.
Appropriate statistical evaluations?	
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	None
Conclusion Remarks	Methylionone did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basic and micronucleus tests. <i>Fd Chem Toxicol.</i> , 21(6), 707-719.

4.3 Repeat dose Toxicity

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
GLP	Ambiguous
Year	1965
Species/strain	Rat/FDRL
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	3.55 mg/kg for males and 4.10 mg/kg for females
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	Groups of 15 FDRL rats (per sex per dose) were given the a test diet containing the test article diluted in cotton-seed oil (2%) a concentration sufficient to provide the predetermined dosage in 3.55 or 4.10 mg/kg bw for 90 days. Animals were housed individually. Body weights and food and water intake were measured weekly. Hematological examination and blood chemical determinations were performed on 8 rats at week 6 and on all rats at week12. At autopsy, liver and kidney weights were measured. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis.
NOAEL (NOEL)	3.55 mg/kg for male and 4.10 mg/kg for females
Toxic Response/effects by Dose Level	No effects observed
Statistical Evaluation	Student t test
Remarks for Results	Males showed slight but not statistically significant reduced hemoglobin level. There was no change in hematocrit or erythrocyte count. The authors concluded that the effect was within control ranges.
Conclusion Remarks	The administration of 3.55 or 4.10 mg/kg of <i>alpha-iso-methylionone</i> to male and female rats, respectively, resulted in no effects based on any measured parameter.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oser B. L., Carson S. and Oser M. (1965) Toxicological tests on Flavor Matters. Food and Cosmetic Toxicology, 3, 563-569.
Substance Name	<i>beta-Ionone</i>

CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methylionone (mixture of isomers), <i>beta</i> -ionone
GLP	Ambiguous
Year	1965
Species/strain	Rat/FDRL
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	11.4 mg/kg for males and 11.6 mg/kg for females
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	Groups of 15 FDRL rats (per sex per dose) were housed individually and given the a test diet containing the test article diluted in cotton-seed oil (2%) a concentration sufficient to provide the predetermined dosage in 3.55 or 4.10 mg/kg bw for 90 days. Animals were housed individually. Body weights and food and water intake were measured weekly. Hematological examination and blood chemical determinations were performed on 8 rats at week 6 and on all rats at week12. At autopsy, liver and kidney weights were measured. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis.
NOAEL (NOEL)	11.4 mg/kg for male and 11.6 mg/kg for females
Toxic Response/effects by Dose Level	No effects observed
Statistical Evaluation	Student t test
Conclusion Remarks	The administration of 11.4 or 11.6 mg/kg of <i>beta</i> -ionone to male and female rats, respectively, resulted in no effects based on any parameter measured.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oser B. L., Carson S. and Oser M. (1965) Toxicological tests on Flavor Matters. Food and Cosmetic Toxicology, 3, 563-569.

Substance Name	<i>alpha</i> -Ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone

GLP	Ambiguous
Year	1965
Species/strain	Rat/FDRL
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	11.8 mg/kg for males and 11.1 mg/kg for females
Exposure Period	90 days
Frequency of Treatment	Continuous
Control Group	Basal diet
Remarks for Test Conditions	Groups of 15 FDRL rats (per sex per dose) were housed individually and given the a test diet containing the test article diluted in cotton-seed oil (2%) a concentration sufficient to provide the predetermined dosage in 3.55 or 4.10 mg/kg bw for 90 days. Animals were housed individually. Body weights and food and water intake were measured weekly. Hematological examination and blood chemical determinations were performed on 8 rats at week 6 and on all rats at week12. At autopsy, liver and kidney weights were measured. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis.
NOAEL (NOEL)	11.8 mg/kg for males and 11.1 mg/kg for females
Toxic Response/effects by Dose Level	No effects observed
Statistical Evaluation	Student t test
Conclusion Remarks	The administration of 11.8 or 11.1 mg/kg of <i>alpha</i> -ionone to male and female rats, respectively, resulted in no effects based on any parameter measured.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oser B. L., Carson S. and Oser M. (1965) Toxicological tests on Flavor Matters. Food and Cosmetic Toxicology, 3, 563-569.

Substance Name	<i>alpha</i> -ionone
CAS No.	127-41-3
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>alpha</i> -ionone
GLP	Yes
Year	1983

Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	10 or 100 mg/kg
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	<p>Groups of Sprague-Dawley rats (15/sex/group) housed in groups of 3 by sex were maintained on diets calculated to result in a daily intake of 10 or 100 mg/kg bw. Body weights and food and water intake were measured every 3rd or 4th day of the study. Hematological examination was performed on rats during weeks 6 and 13 of the study. Blood chemical determinations and urinalysis were performed on weeks 5 and 12. At necropsy, organ weights (brain, liver, spleen, kidneys, caecum, adrenals and gonads (males)) were measured. Histopathological examination of a wide variety of tissues (adrenal, aorta, bladder, brain, caecum, colon, diaphragm, duodenum, epididymis, eye, Harderian gland, heart, ileum, kidney, liver, lung, lymph nodes, mammary, muscle, esophagus, ovary, pancreas, pituitary, prostate, rectum, seminal vesicles, skin, spinal cord, spleen, stomach and testis) were performed for the controls and high dose groups. The liver of the low dose group was also subjected to histopathological examination.</p>
NOAEL (NOEL)	10 mg/kg
LOAEL (LOEL)	100 mg/kg
Toxic Response/effects by Dose Level	<p>The intake of <i>alpha</i>-ionone was determined to be 11 mg/kg bw for males and females at the low dose and 106-108 mg/kg bw at the high dose. Food intake of the high dose group of males and females were significantly lower than controls. A decrease in neutrophils and lymphocytes were reported in males at the high dose levels at week 6 but not at week 13. At the high dose, lower alkaline phosphatase in males and lower glucose levels in females was reported. The relative kidney weights were statistically significantly greater in males at the high dose. Relative and absolute mean liver weights were statistically increased in males at the high dose. The histological finding was desquamation of the thyroid in females at the high dose.</p>
Statistical evaluations	Student t test (white cell counts) and Fisher exact test (histopathological findings)
Conclusion Remarks	The NOEL for <i>alpha</i> -ionone was shown to be 10 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.

References

Gaunt I. F., Butler, W., Ford, G. (1983) The short-term (90 Days) toxicity of *alpha* and *beta*-ionones in rats. Unpublished report to IOFI.

Substance Name	<i>beta</i> -ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methylionone (mixture of isomers), <i>beta</i> -ionone
GLP	Yes
Year	1983
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	10 or 100 mg/kg
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	Groups of Sprague-Dawley rats (15/sex/group) housed in groups of 3 by sex were maintained on diets calculated to result in a daily intake of 10 or 100 mg/kg bw. Body weights and food and water intake were measured every 3rd or 4th day of the study. Hematological examination was performed on rats during weeks 6 and 13 of the study. Blood chemical determinations and urinalysis were performed on weeks 5 and 12. At necropsy, organ weights (brain, liver, spleen, kidneys, caecum, adrenals and gonads (males)) were measured. Histopathological examination of a wide variety of tissues; adrenal, aorta, bladder, brain, caecum, colon, diaphragm, duodenum, epididymis, eye, harderian gland, heart, ileum, kidney, liver, lung, lymph nodes, mammary, muscle, esophagus, ovary, pancreas, pituitary, prostate, rectum, seminal vesicles, skin, spinal cord spleen, stomach and testis were performed for the controls and high dose groups. The liver of the low dose group was also subjected to histopathological examination.
NOAEL (NOEL)	10 mg/kg
LOAEL (LOEL)	100 mg/kg
Toxic Response/effects by Dose Level	The intake of <i>beta</i> ionone was determined to be 11 mg/kg bw for males and females at the low dose and 106-108 mg/kg bw at the high dose. Food intake of the high dose group of males and females were significantly lower than controls. A decrease in erythrocyte counts and hematocrit were reported in males at the high dose levels at week 6 but not at week 13. At the high

Statistical Evaluation	dose, lower alkaline phosphatase in males and lower glucose levels in females was reported. Relative and absolute mean liver weights were statistically increased in males at the high dose. Relative brain, caecal, liver and kidney weights were statistically increased in females at the high dose level. Student t test (white cell counts) and Fisher exact test (histopathological findings)
Conclusion Remarks	The NOEL for <i>beta</i> -ionone was shown to be 10 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Gaunt I. F., Butler, W., Ford, G. (1983) The short-term (90 Days) toxicity of <i>alpha</i> and <i>beta</i> -ionones in rats. Unpublished report to IOFI.

Substance Name	<i>beta</i> -ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for Methyl ionone (mixture of isomers), <i>beta</i> -ionone
Method/guideline	The chemopreventive potency of the test material was studied using the DMBA mammary carcinogenesis model.
GLP	No
Year	1995
Species/strain	Rat/Female Sprague-Dawley
Sex	Female
Route of Administration	Oral-Diet
Doses/concentration Levels	36 mmole/kg (approximately 7400 mg/kg)
Exposure Period	24 weeks
Frequency of Treatment	Continuous
Remarks for Test Conditions	Groups of 32 female rats, including a control group, received diet for 24 weeks. Test material was diluted in corn oil and added to the animal food. A single dose of a suspension of DMBA in sesame oil was given at the end of week 2. Observations were survival, body weight and tumor incidence, latency and multiplicity.
Toxic Response/effects by Dose Level	Ionone delayed the incidence of DBMA-induced tumors in female rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Data from study of antitumorogenicity effects of ionone. Limited data collection.
References	Yu S.G., Anderson, P.J. and Elson, C.E. (1995) Efficacy of <i>beta</i> -ionone in the chemoprevention of rat mammary carcinogenesis. Journal of Agricultural and Food Chemistry,

43(8), 2144-2147.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Surrogate data for methylionone isomer, gamma methylionone in phenyl ethyl alcohol
GLP	Yes
Year	1981
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of Administration	Dermal
Doses/concentration Levels	10 mg/kg
Exposure Period	90 days
Frequency of Treatment	Daily
Control Group	Phenethyl alcohol (1 ml/kg)
Remarks for Test Conditions	1% gamma-Methylionone in phenyl ethyl alcohol at a dose of 10 mg/kg was applied topically to the clipped backs of individually housed Sprague-Dawley rats (5/sex/group) daily for 90 days. A control group of 5 male and female rats received 1 ml/kg phenyl ethyl alcohol. Body weights were measured weekly. Hematological examination, clinical chemistry determinations and urinalysis were performed on all animals at termination. At necropsy, liver and kidney weights were measured and histopathological examination was made of the skin, kidneys, liver, sternal bone, and spinal cord.
NOAEL (NOEL)	10 mg/kg
Toxic Response/effects by Dose Level	No toxic effects were observed at 10 mg/kg bw.
Remarks for Results	Based on measurement of body weight gain, hematological examination, blood chemistry determinations, urinalysis, liver and kidney weights and gross and histopathological examination, there was no difference between test and control groups.
Conclusion Remarks	There was no evidence of toxicity induced by treatment with the gamma methyl ionone.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1981) 90-Day sub acute dermal toxicity in rats. Unpublished report to RIFM.

4.4 Reproductive Toxicity

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Surrogate data for methylionone (mixture of isomers) and <i>alpha</i> -iso-methylionone
Test Type	Two-generation reproduction
GLP	No
Year	1965
Species/Strain	Rats/White adult
Sex	Male and Female
Route of Administration	Oral-Gavage
Duration of Test	8 months
Doses/Concentration	2 mg/day every other day for 8 months
Premating Exposure period for males	Males treated to same regimen, 2mg/day every other day for 8 months
Premating Exposure period for females	2 mg/day every other day until first reproduction at 24 days
Control Group and Treatment	Controls, 0.1 ml oil vehicle every other day
Remarks for Test Conditions	The influence of the test substance on the reproduction was determined in 48 white rats. The females received during 8 months, 0.1 ml oil solution containing 2 mg test substance every other day. Females were followed through 3 reproduction cycles. Females were monitored for number of pregnancies, average weight, number of born offspring, number of offspring born alive, weight at birth and after 7 and 21 days, and viability of offspring after each reproduction. Females received 24 mg before the first reproduction, 84 mg before the second, and 208 mg before the third reproduction. Offspring from the first reproduction (F1) were allowed to reach maturity. This F1 generation received 15 mg ionone prior to reproduction. The F1 generation was then monitored for the same parameters as monitored above.
NOAEL(NOEL)	1 mg/d (8-10 mg/kg/d)
Actual dose received by dose level and sex	2 mg/day every other day
Parental data and F1 as Appropriate	There were no significant differences between any of the parameters monitored for dams, offspring from three reproductions, or offspring of the F1 generation.
Remarks for Results	An average daily intake of 1 mg/day (2 mg/day every other day) or 8-10 mg/kg/day based on average body weight had no effect on dams or pups in repeated reproductions

Conclusion Remarks	No reproductive effects of 8-10 mg/kg/day of ionone in rats.
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to data collected in guidelines study.
References	Sporn A., Schobeschm O., Marin, V., Pansitescu, E. and Runcan, L. (1965) The toxicity of butyl acetate, methyl naphthyl ketone and ionone. <i>Igiena</i> , XII(5), 437-446.

4.5 Developmental/Teratogenicity Toxicity

Substance Name	<i>beta</i> -Ionone
CAS No.	14901-07-6
Remarks for Substance	Data for methylionone homologue, , purity > 99% by HPLC
Method/guideline	Experimental/Retinoid Teratogenicity (Williams, Willhite, 1984)
Test Type	Developmental Toxicity
GLP	No
Year	1986
Species/strain	Hamsters/Golden Syrian
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	14 days (days 1 to 14 of pregnancy)
Doses/concentration Levels	0, 48, 240, or 480 mg/kg
Frequency of Treatment	Single dose on day 8 of pregnancy
Control Group and Treatment	Control group received Tween 20 (0.5 ml/100g)
Remarks for Test Conditions	Timed pregnant LAK:LVG(SYR) hamsters were used. Test material was dissolved in acetone and solubilized in polyoxyethylene sorbitan monolaurate. Final acetone concentration was 5%. Animals received a single dose of test material on day 8 of pregnancy. Fetal and maternal body weights were monitored on day 14. Developmental parameters monitored included number of litters, abnormal litters, implantation sites, number reabsorbed, number abnormal live fetuses, number dead fetuses, mean litter frequency, and characterization of malformations. The median effective Dose for terata and embryonic LD50 were determined.
NOAEL (NOEL) maternal toxicity	480 mg/kg

NOAEL (NOEL) developmental toxicity	480 mg/kg
Actual dose received by dose level and sex	48, 240, or 480 mg/kg
Maternal data with dose level	No observations of toxicity at any dose level. No significant change in body weight in dams at any dose levels compared to controls.
Fetal Data with Dose Level	No significant changes in any fetal parameter measured. No malformations at any dose level.
Appropriate statistical evaluations	Fetal and maternal body weight data by Newman-Keuls test; Number of resorptions by Mann-Whitney test, Number abnormal litters by Yates X2 test
Conclusion Remarks	<p>There was no evidence of developmental or maternal toxicity in golden Syrian hamsters given up to 480 mg/kg of <i>beta</i>-ionone by oral gavage.</p> <p>This study was part of an extensive SAR study that was developed to address retinoid-type teratogenicity reported in humans. The study (Willhite, 1985) is one of numerous studies designed to evaluate the well-recognized Vitamin A-induced teratogenic syndrome in humans leading to characteristic malformations and elevated levels of spontaneous abortions (Benke, 1984; Fernhoff and Iamer, 1984; Rosa, 1984; and Willhite et al., 1986).</p> <p>It was determined that the malformation syndrome observed in humans could be reproduced in fetal hamsters by treating the dam with a high dose of retinoid on Day 8 of gestation (Willhite and Shealy, 1984; Willhite et al., 1984a, 1984b). This protocol evolved from the normal treatment regimen, because it induced malformations in retinoid-treated hamsters at a higher rate than did the normal 6 to 15 daily treatments at slightly lower dose levels. Using this single dose protocol, a series of studies (Willhite and Shealy, 1984; Willhite et al., 1984; Willhite and Balogh-Nair, 1984) were undertaken to investigate the effect of structural changes of Vitamin A on teratogenic activity. Two of the 12 substances chosen for the study were <i>beta</i>-ionone, a retinoid-degradation product containing a 4-carbon side chain and pseudoionone, a ring opened analog containing the same functional groups and molecular formula as ionone. The results of studies on numerous compounds indicate that teratogenic potential is associated with specific structural features in the Vitamin A. The presence of the following structural requirements:</p> <ol style="list-style-type: none"> 1) a retinoid beta-cyclohexenylidene ring, 2) a polyene chain of at least five carbons, 3) a polar hydrophilic function group located on the polyene chain terminus, and 4) a trans stereochemistry in the polyene chain giving rise to a curved plane in the chain. <p>Structural requirements 2, 3, and 4 were not met by <i>beta</i>-ionone while structural requirements 1-4 were not met by pseudoionone. Neither substance showed any evidence of teratogenicity in hamsters at dose levels up to 960 or 480 mg/kg, respectively. Given these results and well-documented protocol capable of identifying teratogenic potential in this group of substances, an additional developmental study using an OECD 421 or 414 protocol is not warranted at this time. In</p>

addition, ionone derivatives are readily metabolized via reduction of the ketone function and allylic oxidation of exocyclic methyl substituents to yield in both cases, polar excretable metabolites. Given the metabolic fate of this class of substances and the comprehensive developmental testing for carotenoid teratogenicity, there is no basis to perform additional developmental testing for members of this category.

Data Qualities Reliabilities Reliability code 2. Reliable with restriction.

Remarks for Data Reliability Code 2. Basic data given: comparable to guidelines/standards.

References Willhite C.C (1986) Structure-activity relationships of retinoids in developmental toxicology. II. Influence of the polyene chain of the vitamin A molecule. Toxicology and Applied Pharmacology, 83, 563-575.

Substance Name	Pseudoionone
CAS No.	141-10-6
Remarks for Substance	Data for methylionone homologue, pseudoionone, purity > 98% by HPLC
Method/guideline	Experimental/Retinoid Teratogenicity (Williams, Willhite, 1984)
Test Type	Developmental Toxicity
GLP	No
Year	1986
Species/strain	Hamsters/Golden Syrian
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	14 days (days 1 to 14 of pregnancy)
Doses/concentration Levels	0, 96, or 960 mg/kg
Frequency of Treatment	Single dose on day 8 of pregnancy
Control Group and Treatment	Control group received Tween 20 (0.5 ml/100g)
Remarks for Test Conditions	Timed pregnant LAK:LVG(SYR) hamsters were used. Test material was dissolved in acetone and solubilized in polyoxyethylene sorbitan monolaurate. Final acetone concentration was 5%. Animals received a single dose of test material on day 8 of pregnancy. Fetal and maternal body weights were monitored on day 14. Developmental parameters monitored.
NOAEL (NOEL) maternal toxicity	96 mg/kg
LOAEL(LOEL) maternal toxicity	960 mg/kg

NOAEL (NOEL)	960 mg/kg
developmental toxicity	
Actual dose received by dose level and sex	96 or 960 mg/kg
Maternal data with dose level	The maternal body weight was significantly depressed following treatment with 960 mg/kg of pseudoionone.
Fetal Data with Dose Level	No significant changes in any fetal parameter measured No malformations at any dose level
Appropriate statistical evaluations	Fetal and maternal body weight data by Newman-Keuls test, Number. of resorptions by Mann-Whitney test, Number abnormal litters by Yates X2 test.
Conclusion Remarks	There was no evidence of developmental toxicity at doses up to an including 960 mg/kg and maternal toxicity at 96 mg/kg in golden Syrian hamsters (See discussion for <i>beta</i> -ionone above).
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Willhite C.C (1986) Structure-activity relationships of retinoids in developmental toxicology. II. Influence of the polyene chain of the vitamin A molecule. Toxicology and Applied Pharmacology, 83, 563-575.