Piperitone

Toxicity monograph (with existing HCVs)

May 2018

Prepared by:

TABLE OF CONTENTS

(b) (4)

Version 1

Piperitone

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of piperitone (CAS RN[1] 89-81-6), focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. CAS RN 89-81-6 refers to the unspecified enantiomer; data on the individual L- and D- enantiomers (CAS RNs 4573-50-6 and 6091-50-5, respectively) were also considered relevant. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

EXPERTISE

(b) (4)

TOXICITY DATA SEARCH CRITERIA[3]

(b) has access to a wide range of data sources, including the (b) (4) (see the Appendix for details), PubMed, the TOXNET system of databases and databanks (which includes Toxline (the toxicity subset of Medline), HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB), and eChemPortal. In addition, the industry-submitted REACH registration dossiers[4] (where available) disseminated on the ECHA website were consulted for critical ADME[5] and/or toxicity data, and also for derived no-effect levels (DNELs).

All searches were conducted in May 2018 using the CAS RNs and (in PubMed only) names and synonyms identified below, as appropriate.

The data summarised in this report refers to the unheated form unless otherwise stated.

---

[1] Chemical Abstracts Service Registry Number.

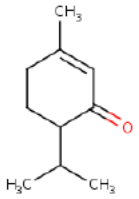
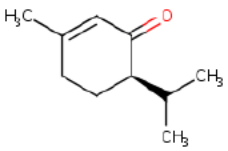
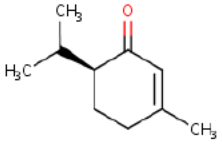
(b) (4)

[3] Disclaimer: searches are valid and complete as of the date of searching (b) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

[4] Information on Registered Substances comes from registration dossiers which have been assigned a registration number. The assignment of a registration number does however not guarantee that the information in the dossier is correct or that the dossier is compliant with Regulation (EC) No 1907/2006 (the REACH Regulation). This information has not been reviewed or verified by the Agency or any other authority. The content is subject to change without prior notice.

[5] Absorption, Distribution, Metabolism and Excretion.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier			
Name	Piperitone	L-Piperitone	D-Piperitone
Synonyms	3-Carvomenthenone; 6-Isopropyl-3-methylcyclohex-2-enone; p-Menth-1-en-3-one	(R)-6-(Isopropyl)-3-methylcyclohex-2-en-1-one	-
CAS RN	89-81-6	4573-50-6	6091-50-5
REACH registration number[6]	01-2120098646-40-xxxx	01-2120760173-60-xxxx	Not REACH registered
Molecular formula	$C_{10}H_{16}O$		
Molecular weight	152.24		
Structure			
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available	**Harmonised classification:** Not available	**Harmonised classification:** Not available
	REACH joint registrants: "Not classified"	**REACH joint registrants:** Skin Irrit. 2 (H315): Causes skin irritation. Eye Irrit. 2 (H319): Causes serious eye irritation. Skin Sens. 1B (H317): May cause an allergic skin reaction.	**REACH joint registrants:** Not available

A further CAS RN (58615-39-7) referring to "isopiperitone", which appears to have an identical structure to piperitone, was identified and used in the data searches described.

[6] REACH registration numbers are substance and company specific. Therefore, the substance-specific part of the registration number is included here, from data disseminated on the ECHA 'registered substance' website.

ADME

No relevant data were identified on the ADME of piperitone.

In an evaluation of 22 structurally-related secondary alicyclic saturated and unsaturated alcohols, ketones and esters containing secondary alicyclic alcohols [including L-piperitone, CAS RN 4573-50-6], the European Food Safety Authority concluded that "one of the main pathways for the candidate alcohols and the ketones (after reduction)" … "is conjugation with glucuronic acid followed by excretion" … "Thus, it may be anticipated that these 22 substances will be metabolised to innocuous products" (EFSA, 2015a). This supports a previous opinion from the Joint FAO/WHO Expert Committee on Food Additives that L-piperitone is "anticipated to be reduced to the corresponding alcohol, primarily conjugate with glucuronic acid and be excreted in the urine" (JECFA, 2009).

A similar conclusion was previously reached for "piperitone" (given as CAS RN 6091-50-5, which applies to D-piperitone): "the ketones" … "in this group would be reduced to their corresponding secondary alcohols, which, like menthol, would be conjugated with glucuronic acid and then excreted in the urine" (JECFA, 1999).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified on piperitone or on its enantiomers.

Skin irritation

Expert-group opinion

No substance-specific data were identified on piperitone or on its enantiomers.

Human (*in vivo*)

No irritation was seen in 27 subjects following a 48-hour covered skin application of piperitone [CAS RN not specified] at 10% in petrolatum (Epstein, 1975). [See also Skin sensitisation section.]

Human (*in vitro*)

In vitro test methods using human skin models are available in the REACH dossier on (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one (CAS RN 4573-50-6).

In the first *in vitro* test, which was according to the dossier submitters was conducted in accordance with OECD Test Guideline 431[7], and to GLP[8], duplicate reconstructed three-dimensional human epidermis samples were exposed to 50 µL "piperitone" [not further specified, but presumably CAS RN 4573-50-6] at 79.4 µL/cm² for 3 minutes or 1 hour. Viability (from relative absorbance) did not decrease after the 3-minute exposure and was reduced to

[7] *In Vitro* Skin Corrosion: Human Skin Model Test.
[8] Good Laboratory Practice.

56.7% after the 1-hour exposure. Based on these results, "piperitone" was not considered to be corrosive[9] (Anon., 2016a).

The second *in vitro* skin irritation test was said to have been conducted in accordance with OECD Test Guideline 439[10] and to GLP. Triplicate samples of reconstructed human skin were exposed to 30 µL of the test substance [presumably CAS RN 4573-50-6] at a concentration of 47 µL/cm^2 for 1 hour. After treatment, the tissue viability decreased to 4.8% compared to the negative control. On this basis, the test substance was considered irritating[11] (Anon., 2016b).

Non-human

Moderate skin irritation was observed when undiluted piperitone [CAS RN not specified] was applied to the intact or abraded skin of an unspecified number of rabbits for 24 hours under occlusion (Moreno, 1975).

Eye irritation

Expert-group opinion

No substance-specific data were identified on piperitone or on its enantiomers.

Human

No substance-specific data were identified on piperitone or on its enantiomers.

Non-human

The REACH dossier on (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one (CAS RN 4573-50-6) notes that an eye irritation study has been conducted in compliance with OECD Test Guideline 405[12] and GLP. One hour after the instillation of 0.1 mL of the undiluted test article [presumably CAS RN 4573-50-6] to one eye of each of four female rabbits, various signs of irritation (conjunctival redness, corneal opacity, iritis, swelling) were present in all exposed animals. These effects were reversible and the eyes were considered 'normal' by day 7. On this basis, the test substance was considered an eye irritant (Anon., 2000).

Other local effects

No substance-specific data were identified on piperitone or on its enantiomers.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified on piperitone or on its enantiomers.

Skin sensitisation

Expert-group opinion

No substance-specific data were identified on piperitone or on its enantiomers.

[9] The threshold for corrosivity was considered to be 50% after 3 minutes and 15% after 1 hour.
[10] *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method.
[11] The threshold for irritancy was considered to be 50%.
[12] Acute Eye Irritation/Corrosion.

Human (*in vivo*)

In a maximisation test[13], no skin sensitisation reactions were produced when 27 subjects were tested with piperitone [CAS RN not specified] at 10% in petrolatum (Epstein, 1975). [See also Skin irritation section.]

One woman and one of two men with allergic contact dermatitis to peppermint oil reacted to a patch test with piperitone [CAS RN not specified] at 1% in petrolatum (Saito and Oka, 1990). [No further details are available from the English abstract and tables of this Japanese paper.]

Human (*in vitro*)

The REACH dossier for (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one (CAS RN 4573-50-6) includes two *in vitro* studies and an *in chemico* test. The *in vitro* work comprises a human cell line activation test (h-CLAT) performed in accordance with OECD Test Guideline 442E[14] and GLP, which found evidence of dendritic cell activation (a key event in the skin sensitisation adverse outcome pathway) by the test substance [presumably CAS RN 4573-50-6] (Anon., 2016c). A KeratinoSens™ assay, using an immortalised adherent human keratinocyte cell line and conducted in accordance with OECD Test Guideline 442D[15] and GLP, also found evidence (increased luciferase activity) for the activation of keratinocytes, another key event, however "due to interference of the test item with the test system[16] the test has to be considered as inconclusive" (Anon., 2017a). The *in chemico* direct peptide reactivity assay (DPRA) (OECD Test Guideline 442C[17]) found minimal reactivity for the test substance (3.23%; less than the cut-off for a positive result of 6.38%) (Anon., 2017b).

Non-human

A local lymph node assay (LLNA) is described in the REACH dossier for (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one (CAS RN 4573-50-6), conducted in accordance with OECD Test Guideline 442B[18] and GLP. Groups of five female CBA/N mice were topically treated with 25 µL of the test substance [presumably CAS RN 4573-50-6] on each ear at concentrations of 0, 5, 25 or 100% in acetone/olive oil for three consecutive days. The SI values were significant (≥1.6[19]) for the 25 and 100% test concentrations, but there was no significant increase in lymphoproliferation for the 5% concentration. The EC1.6 value[20] was calculated to be 16.6%. This test method was considered to show "indications of skin sensitising potential" for CAS RN 4573-50-6 (Anon., 2017c).

[13] The test procedure typically involves an initial induction phase of five 48-hour covered patch tests, followed 10-14 days later by a 48-hour covered challenge patch.
[14] *In Vitro* Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation.
[15] *In Vitro* Skin Sensitisation: ARE-Nrf2 Luciferase Test Method.
[16] Concentrations inducing a luciferase activity >1.5 also had an increased cell viability (as shown by metabolic activity) above >150%, which according to the dossier submitters "indicates interference of the test item with the test system and might be related to a cellular stress reaction".
[17] In Chemico Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA).
[18] Skin Sensitization: Local Lymph Node Assay: BrdU-ELISA.
[19] OECD test guideline 442B defines stimulation index (SI) as "the ratio of the proliferation in treated groups to that in the concurrent vehicle control group". An SI of ≥1.6 is considered positive under this test method.
[20] i.e. the concentration giving rise to an SI of 1.6.

Oral allergy/intolerance

No substance-specific data were identified on piperitone or on its enantiomers.

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS

Single dose toxicity

No substance-specific data were identified on piperitone or on its enantiomers.

Repeated dose toxicity

No substance-specific data were identified on piperitone or on its enantiomers.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Expert-group opinion

No substance-specific data were identified on piperitone or on its enantiomers.

Human

No substance-specific data were identified on piperitone or on its enantiomers.

Non-human

The REACH dossier on (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one (CAS RN 4573-50-6) describes an acute oral test using the "acute toxic class" method, conducted in compliance with OECD Test Guideline 423[21] and GLP. Two groups of three female Sprague-Dawley rats per dose (i.e. a total of six females/dose) were sequentially given the test substance [presumably CAS RN 4573-50-6] at 300 or 2000 mg/kg bw by gavage (in corn oil). No deaths were seen at either dose, and the oral LD_{50} value[22] (from the flow-chart in the relevant OECD Guideline) was predicted to be >5000 mg/kg bw (Anon., 2016d).

An acute oral LD_{50} value of 3550 mg/kg bw has been reported in rats for piperitone [CAS RN not specified] (Moreno, 1975).

The dermal LD_{50} value was >5000 mg/kg bw in rabbits given a [presumably occluded] skin application of piperitone [CAS RN not specified] for an unspecified duration (Moreno, 1975). [No further details are given in the citing source.]

The subcutaneous LD_{50} value for mice given piperitone [CAS RN not specified] in sesame oil was 1420 mg/kg bw (Wenzel and Ross, 1957).

The "absolute lethal dose" in seven dogs receiving a slow intravenous infusion of piperitone [CAS RN not specified] was 400 mg/kg bw (Caujolle and Roux, 1954).

[21] Acute Oral toxicity - Acute Toxic Class Method.

[22] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.

Repeated dose toxicity

No substance-specific data were identified on piperitone or on its enantiomers.

GENOTOXICITY

Expert-group opinions

In its evaluation of 22 structurally-related α,β-unsaturated alicyclic ketones and precursors, EFSA (2015b) concluded that a concern for genotoxicity could be ruled out for piperitone (CAS RN 89-81-6) and L-piperitone (CAS RN 4573-50-6) based on experimental data on another member of the group, isophorone (CAS RN 78-59-1). Part of EFSA's evaluation included quantitative structure-activity relationship (QSAR) work on the two piperitone chemicals[23].

Mammals (*in vivo*)

No substance-specific data were identified on piperitone or on its enantiomers.

Mammalian cells (*in vitro*)

No substance-specific data were identified on piperitone or on its enantiomers.

Micro-organisms

The REACH dossier on (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one (CAS RN 4573-50-6) has described a bacterial reverse mutation assay on the test substance [presumably CAS RN 4573-50-6], performed to GLP and OECD Test Guideline 471[24]. There was no mutagenicity seen in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537, or in *Escherichia coli* strain WP2*uvr*A (with or without metabolic activation by S9 mix[25]) at test doses of up to 5000 µg/plate (Anon., 2016e).

Piperitone [CAS RN not specified] was not mutagenic when tested at 3 µmol/plate in a limited assay (spot test) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1536. The test was performed in the presence and absence of metabolic activation by S9 (Florin *et al.*, 1980). [The study is limited in that only a single low concentration was tested (with no evidence of cytotoxicity or precipitation) in only four bacterial strains (rather than five)[26].]

Other

No substance-specific data were identified on piperitone or on its enantiomers.

---

[23] Piperitone was: -ve for MultiCASE Ames test and MultiCASE Chromosomal aberration test in CHO cells; +ve in MultiCASE Mouse lymphoma test; "Out of applicability domain" for ISS Local Model Ames Test TA100 and MultiCASE chromosome aberration test in CHL cells. L-Piperitone was: -ve for MultiCASE Ames test and MultiCASE Chromosomal aberration test in CHO cells; Equivocal for MultiCASE chromosome aberration test in CHL cells; "Out of applicability domain" for ISS Local Model Ames Test TA100 and MultiCASE Mouse lymphoma test.

[24] Bacterial Reverse Mutation Test.

[25] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.

[26] The relevant OECD Test Guideline (471 - Bacterial Reverse Mutation Test) also recommends testing in Salmonella TA102 or *E. coli* strain WP2*uvr*A or WP2*uvr*A (pKM101).

CARCINOGENICITY

No substance-specific data were identified on piperitone or on its enantiomers.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No substance-specific data were identified on piperitone or on its enantiomers.

CARDIOPULMONARY EFFECTS[27]

No relevant substance-specific data were identified on piperitone or on its enantiomers.

OTHER TOXICITY CONSIDERATIONS

Intraperitoneal injection of piperitone [CAS RN not specified] (in sesame oil) at 0, 50, 100, 200 or 400 mg/kg bw led to a dose-related increase in running activity in groups of four black-hooded male rats (Wenzel and Ross, 1957).

Administering[28] piperitone [CAS RN not specified] to mice at 100 mg/kg bw produced some diuretic action (Morimoto and Shibata, 2010).

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific inhalation HCVs were identified on piperitone or on its enantiomers.

EFSA has concluded that piperitone (CAS RN 89-81-6) is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive. At the time of the EFSA review, these were 10 and 44 µg/person/day[29] in the EU (EFSA, 2015b).

EFSA, and previously JECFA, also concluded that L-piperitone (CAS RN 4573-50-6) is of "no safety concern" at 12 µg/person/day in the EU (EFSA, 2015a,b) or at 0.01 or 17 µg/person/day in the EU and US, respectively (JECFA, 2009).

"Piperitone" (CAS RN 6091-50-5, which applies to D-piperitone) was of "no safety concern" to JECFA at ('current') estimated levels of dietary intake as a food additive of 51 µg/day in the EU and 10 µg/day in the US (JECFA, 1999).

[27] Potential effects on the heart, blood vessels and/or respiratory tract.
[28] The route is not obvious from the English abstract or tables of this Japanese study.
[29] Both figures are provided, it is not clear what they relate to as both come under the heading of "MSDI".

REFERENCES

Anon. (2000). Eye irritation. 001 Key experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/4/3 [Cited in Symrise AG, 2018.]

Anon. (2016a). Skin irritation / corrosion. 001 Key experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/4/2 [Cited in Symrise AG, 2018.]

Anon. (2016b). Skin irritation / corrosion. 002 Key experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/4/2/?documentUUID=49dfa44f-786f-4c52-8f46-8de97307043b [Cited in Symrise AG, 2018.]

Anon. (2016c). Skin sensitisation. 001 Weight of evidence experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/5/2/?documentUUID=9c043df9-d3f2-4ed2-9b5a-01bbba21b988 [Cited in Symrise AG, 2018.]

Anon. (2016d). Acute toxicity: oral. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/3/2 [Cited in Symrise AG, 2018.]

Anon. (2016e). Genetic toxicity: in vitro. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/7/2 [Cited in Symrise AG, 2018.]

Anon. (2017a). Skin sensitisation. 003 Weight of evidence experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/5/2/?documentUUID=9a5f2875-d0e7-40a9-beb7-129dac278c56 [Cited in Symrise AG, 2018.]

Anon. (2017b). Skin sensitisation. 002 Weight of evidence experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/5/2/?documentUUID=403854ea-955b-4d3d-b7cd-cf010d27e3b4 [Cited in Symrise AG, 2018.]

Anon. (2017c). Skin sensitisation. 004 Weight of evidence experimental result. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/7/5/2/?documentUUID=5e523c63-6810-4c5c-94c4-32c369459950 [Cited in Symrise AG, 2018.]

Caujolle F and Roux G (1954). [Immediate toxicity of carvomenthone, carvone, piperitone and piperitenone.] Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences 239, 680-681.

EFSA (2015a). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 9, Revision 6 (FGE.09Rev6): Secondary alicyclic saturated and unsaturated alcohols, ketones and esters containing secondary alicyclic alcohols from chemical group 8 and 30, and an ester of a phenol derivative from chemical group 25. EFSA Journal 13(9), 4243. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4243

EFSA (2015b). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 212, Revision 3 (FGE.212Rev3): α,β-Unsaturated alicyclic ketones and precursors from chemical subgroup 2.6 of FGE.19. EFSA Journal 13(5), 4116. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4116/epdf

Epstein WL (1975). Report to RIFM, 3 June [cited in Opdyke, 1978].

Florin I, Rutberg L, Curvall M and Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15, 219-232.

JECFA (1999). Safety evaluation of certain food additives. Prepared by the fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 42. http://www.inchem.org/documents/jecfa/jecmono/v042je01.htm

JECFA (2009). Safety evaluation of certain food additives. Prepared by the sixty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 60. http://www.inchem.org/documents/jecfa/jecmono/v60je01.pdf

Moreno OM (1975). Report to RIFM, 11 April [cited in Opdyke, 1978].

Morimoto Y and Shibata Y (2010). Effects of various fragrant ingredients on desmopressin-induced fluid retention in mice. Yakugaku Zasshi 130(7), 983-987.

Opdyke DLJ (1978). Monographs on Fragrance Raw Materials: Piperitone. Food and Cosmetics Toxicology 16, 863-864.

Saito F and Oka K (1990). Allergic contact dermatitis due to peppermint oil. Skin Research 32, 161-167.

Symrise AG (2018). REACH dossier on (R)-6-(isopropyl)-3-methylcyclohex-2-en-1-one. Updated March 2018. https://echa.europa.eu/registration-dossier/-/registered-dossier/22738/1

Wenzel DG and Ross CR (1957). Central stimulating properties of some terpenones. Journal of the American Pharmaceutical Association 64, 77-82.

APPENDIX: The (b) (4) database and databank

(b) (4)

(b) (4) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, (b) (4) covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (e.g. COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- (b) (4)