(b) (4)

3-Methylvaleric acid

Toxicity monograph (with existing HCVs)

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of 3-methylvaleric acid (CAS RN[1] 105-43-1), focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

EXPERTISE

(b)(4) was founded[2] in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have been working together for many years (more than 40 years in some instances) and have a record of objectivity and scientific excellence. All senior and principal scientists in the current team are accredited and listed in the European (Eurotox) and UK Royal Society of Biology/British Toxicology Society Registers of Toxicologists and are thus bound by their specific codes of conduct.

TOXICITY DATA SEARCH CRITERIA[3]

(b) has access to a wide range of data sources, including the unique (b) (4) databank (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.

All searches were conducted in May 2018 using the CAS RN and (in PubMed only) name and synonym identified below, as appropriate.

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

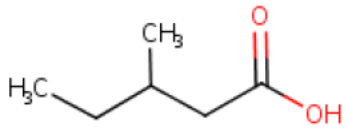
IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	3-Methylvaleric acid
Synonyms	3-Methylpentanoic acid
CAS RN	105-43-1

[1] Chemical Abstracts Service Registry Number.

[2] (b)(b) (4)

[3] Disclaimer: searches are valid and complete as of the date of searching. (b) (4) no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

REACH registration number[4]	Not REACH registered
Molecular formula	$C_6H_{12}O_2$
Molecular weight	116.16
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available
	REACH joint registrants: Not available

ADME[5]

No substance-specific data were identified on the ADME of inhaled 3-methylvaleric acid.

An assessment from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) noted that "in general, branched-chain aliphatic acyclic alcohols, aldehydes and acids are rapidly absorbed from the gastrointestinal tract". Of the 22 structurally-related methyl-substituted alcohols, aldehydes, and carboxylic acids [including 3-methylvaleric acid], "all the compounds were predicted to be metabolized to innocuous products" (JECFA, 1998).

"The metabolism of 3-methylpentanoic acid has been studied in mammals. alpha-Oxidation and decarboxylation of 3-methylpentanoic acid would yield 2-methylbutyric acid followed by β-oxidative cleavage to yield acetyl CoA and acetone. In guinea-pig liver homogenate, 3-methylpentanoic acid is converted to 2-methylbutyric acid which is further metabolized via β-oxidative cleavage. In rabbits, 3-methylpentanoic acid is converted to β-hydroxybutyric acid" (JECFA, 1998).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

Skin irritation

No substance-specific data were identified.

[4] 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.
[5] Absorption, Distribution, Metabolism and Excretion.

Eye irritation
No substance-specific data were identified.

Other local effects
No substance-specific data were identified.

SENSITISATION AND INTOLERANCE
Respiratory tract sensitisation
No substance-specific data were identified.

Skin sensitisation
No substance-specific data were identified.

Oral allergy/intolerance
No substance-specific data were identified.

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS
Single dose toxicity
No substance-specific data were identified.

Repeated dose toxicity
No substance-specific data were identified.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES
Single dose toxicity
Expert-group opinion
No substance-specific data were identified.

Human
No substance-specific data were identified.

Non-human
An oral LD_{50} value[6] of >700 mg/kg bw was reported for rats (Vollmuth *et al.*, 1989).

Repeated dose toxicity
Expert-group opinion
No substance-specific data were identified.

Human
No substance-specific data were identified.

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

Non-human

No standard good-quality repeated-dose studies on 3-methylvaleric acid were identified. Some oral studies are discussed below, with a limited assessment of general systemic toxicity.

Groups of 20 female CD-1 rats were administered 3-methylvaleric acid in corn oil by oral gavage for 5 days at 0, 175, 350 or 700 mg/kg bw/day. On day 3, a culture of *Listeria monocytogenes* was injected into the tail vein, and the rats were observed for 10 days. No adverse effects were seen on mortality, body weight or clinical signs of toxicity (Gaworski *et al.*, 1994). [See also Other toxicity considerations section.]

Groups of ten female CD-1 rats were given 3-methylvaleric acid in corn oil by gavage for 5 days at 0, 175, 350 or 700 mg/kg bw/day. Rats were injected with sheep red blood cells (SRBCs) and examined for spleen cell viability 4 days later. No adverse effects on body, spleen or thymus weights were seen (Gaworski *et al.*, 1994). [See also Other toxicity considerations section.]

GENOTOXICITY

No substance-specific data were identified.

CARCINOGENICITY

No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Expert-group opinions

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No standard substance-specific reproductive or developmental toxicity data were identified.

Dawson *et al.* (1996) report that 3-methylpentanoic acid is a 'moderate' developmental toxicity hazard, based on FETAX (Frog Embryo Teratogenesis Assay: Xenopus). [The relevance of this assay to mammalian systems is unclear.]

CARDIOPULMONARY EFFECTS[7]

No substance-specific data were identified.

[7] Potential effects on the heart, blood vessels and/or respiratory tract.

OTHER TOXICITY CONSIDERATIONS

Two studies focused on immunotoxicity are available on 3-methylvaleric acid.

In a host-resistance assay, groups of 20 female CD-1 rats were given 3-methylvaleric acid in corn oil by oral gavage for 5 days at 0 or up to 700 mg/kg bw/day. On day 3, a culture of *L. monocytogenes* was injected into the tail vein, and the rats were observed for 10 days. There was no difference in resistance to bacterial infection, or in the spleen cell viability of test and control rats (Gaworski *et al.*, 1994). [See also Toxicity studies – Other exposure routes section.]

In an assay for humoral immunity, groups of ten female CD-1 rats were administered 3-methylvaleric acid in corn oil by gavage for 5 days at 0 or up to 700 mg/kg bw/day, and were injected with SRBCs and examined for spleen cell viability 4 days later. No immunotoxic effects were observed (Gaworski *et al.*, 1994). [See also Toxicity studies – Other exposure routes section.]

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific inhalation HCVs were identified.

JECFA has concluded that 3-methylvaleric acid is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive. At the time of the JECFA review, these were 2.9 or 8.8 µg/person/day in the EU and US, respectively (JECFA, 1998).

REFERENCES

Dawson DA, Schultz TW and Hunter RS (1996). Developmental toxicity of carboxylic acids to Xenopus embryos: a quantitative structure-activity relationship and computer-automated structure evaluation. Teratogenesis, Carcinogenesis, and Mutagenesis 16, 109-124.

Gaworski CL, Vollmuth TA, Dozier MM, Heck JD, Dunn LT, Ratajczak HV and Thomas PT (1994). An immunotoxicity assessment of food flavouring ingredients. Food and Chemical Toxicology 32, 409-415.

JECFA (1998). Safety evaluation of certain food additives and contaminants. Prepared by the forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series 40.
http://www.inchem.org/documents/jecfa/jecmono/v040je01.htm

Vollmuth TA, Heck JD, Ratajczak HV and Thomas PT (1989). Immunotoxicity assessment of flavoring ingredients using a rapid and economical screen. Toxicologist 9, 206 [cited in JECFA, 1998].

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

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(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) Toxicity Profiles