IARC MONOGRAPHS

SOME CHEMICALS PRESENT IN INDUSTRIAL AND CONSUMER PRODUCTS, FOOD AND DRINKING-WATER

VOLUME 101

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 15-22 February 2011

LYON, FRANCE - 2013

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

2,4-HEXADIENAL

1. Exposure Data

1.1 Chemical and physical data

From Ford *et al.* (1988), NTP (2003) and HSDB (2010)

1.1.1 Nomenclature

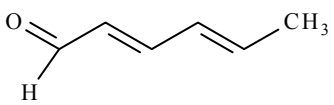
(a) E,E- isomer

Chem. Abstr. Services Reg. No.: 142-83-6
Chem. Abstr. Name: 2,4-Hexadienal, (*E*,*E*)-
IUPAC Name: (2*E*,4*E*)-Hexa-2,4-dienal
EINECS No.: 205-564-3
JECFA: 1175
Flavouring No.: 05.057
Synonyms: Hexa-2,4-dienal; 2,4-hexadienal, (2*E*,4*E*)-; *trans*,*trans*-2,4-hexadienal; 2,4-hexadien-1-al; (*E*,*E*)-2,4-hexadien-1-al; *trans*,*trans*-2,4-hexadien-1-al; 1,3,-pentadiene-1-carboxaldehyde; 2-propyleneacrolein; 2-propylene acrolein; 3-propyleneacrolein; sorbaldehyde; sorbic aldehyde

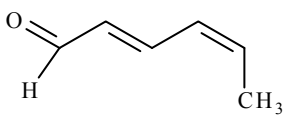
(b) E,Z isomer

Chem. Abstr. Services Reg. No.: 53398-76-8
Chem. Abstr. Name:
(2*E*,4*Z*)-2,4-Hexadienal
Synonym: trans,*cis*-2,4-Hexadienal

1.1.2 Structural and molecular formulae and relative molecular mass



(E,E)-2,4-Hexadienal



(2*E*,4*Z*)-2,4-Hexadienal

C_6H_8O
Relative molecular mass: 96.13

1.1.3 Chemical and physical properties of the pure substance

Throughout the *Monograph*, when not otherwise specified, 2,4-hexadienal refers to the compound for which the stereoisomeric status has not been indicated.

Description: Colourless liquid with a sweet, green, spicy, floral or citrus odour
Boiling-point: 174 °C at 15 mm Hg; 76 °C at 30 mm Hg
Specific gravity: 0.898 at 25 °C
Vapour pressure: 4.8 mm Hg at 25 °C (estimated)
Refractive index: 1.5384 at 20 °C
Solubility: Insoluble in water; soluble in ethanol

Flash-point: 54.4 °C
Odour threshold: 0.0018 g/m^3
Octanol/water partition coefficient: log K_{ow}, 1.37 (estimated)
Henry's law constant:
9.78×10^{-6} atm.m^3/mol at 25 °C

1.1.4 Technical products and impurities

2,4-Hexadienal is commercially available as a > 95% pure mixture of *trans*,*trans* (≈80%) and *cis*,*trans* (10–16%) isomers with the Chemical Abstract Services Registry Number 80466-34-8.

α-Tocopherol (at 0.50%) is present as an additive in 2,4-hexadienal (Bedoukian Research Inc., 2010).

1.1.5 Analysis

No data were available to the Working Group.

1.2 Production and use

1.2.1 Production

2,4-Hexadienal is prepared by the condensation of acetaldehyde (Ford *et al.*, 1988). Current production levels are not available.

1.2.2 Use

2,4-Hexadienal is used as a flavouring agent in the manufacture of the aromatic chemical 3,5,7-nonatrien-2-one, as a chemical intermediate in various organic synthetic reactions and as a raw material in the manufacture of sorbic acid (a widely used food preservative). It is also used as a chemical intermediate in the manufacture of polymethine dyes, as a pharmaceutical intermediate in the manufacture of mitomycins and antihypercholesteraemics, as an inhibitor of corrosion for steel used in oil field operations, as a monomer in reactions with silane comonomers for the manufacture of polyalkenyloxysilane polymer and as a fumigant against larvae of the Caribbean fruit fly (NTP, 2003).

1.3 Occurrence

1.3.1 Natural occurrence

2,4-Hexadienal is one of the unsaturated aldehydes that are naturally present as auto-oxidation products of polyunsaturated fatty acids (PUFAs) of plant and animal origin (NTP, 2003).

1.3.2 Occupational exposure

Exposure to 2,4-hexadienal may occur from its inhalation and through dermal contact at workplaces during its production or use.

1.3.3 Dietary exposure

(a) Natural occurrence in food or development during storage or processing

According to Burdock (2005), 2,4-hexadienal, (*E*,*E*)- has been detected in olives, tomatoes, caviar, fish, auto-oxidized salmon oil, tea, apricots, strawberries, wheaten bread, Russian cheeses, cooked chicken and beef, boiled mutton, hop oil, raw and roasted peanuts, soya beans, rice, buckwheat, malt, kiwi fruit and scallops. The Council of Europe (2000) reported concentrations of 0.001–0.003 mg/kg 2,4-hexadienal, (*E*,*E*)- in roasted peanuts and 0.0004 mg/kg in kiwi fruit. Quantitative data in the Netherlands database of volatile compounds in food reported highest concentrations of 2,4-hexadienal in apricots (0–0.2 mg/kg), tomatoes (0.186–0.282 mg/kg) and chicken (0.2 mg/kg); lower concentrations were reported in fish (0.03 mg/kg) and malt (< 0.01–0.02 mg/kg). Much lower concentrations were reported in peanuts (0.0005–0.003 mg/kg) and kiwi fruit (0.0004 mg/kg). In addition, qualitative data are available for beef, buckwheat, caviar, various cheeses, guava and feyoa, hop oil, lamb and mutton, olives, rice, scallops, soya

beans, strawberries, thyme and wheaten bread (TNO, 2010).

According to a review (NTP, 2003), 2,4-hexadienal, (*E*,*E*)- occurs naturally in tomatoes, mangoes, kiwi fruit and Chinese quince. It has been detected in cow's milk fat, potato chips, bread crusts, tropical fruit, herbs and spices, in the essential oils of lovage, thyme leaf and dill and in solid alfalfa extract.

2,4-Hexadienal was identified as one of the volatile flavour components of *Callicarpa japonica Thunb.*, which belongs to the Verbenaceae family and is indigenous to Japan, the Republic of Korea, the People's Republic of China, and Taiwan, China (Kim & Shin, 2004).

During cooking, the auto-oxidation process in oil and fat is enhanced. The concentration of PUFA-derived auto-oxidation products generated depends on the PUFA content of the oil, the nature and capacity of the heating vessel used (surface area), and the durations and conditions of heating and storage (Haywood *et al.*, 1995). The oxidative deterioration of glycerol-bound PUFAs in culinary oils and fats during episodes of heating associated with normal usage (30–90 minutes at 180 °C) has been studied (Claxson *et al.*, 1994). Thermal stressing of PUFA-rich culinary oils was found to generate high levels of aldehydes, whereas only low concentrations were produced in oils with a low PUFA content, lard and dripping subjected to the above-mentioned heating episodes. Samples of repeatedly used, PUFA-rich culinary oils obtained from restaurants also contained high levels of each class of aldehyde. Auto-oxidation occurs in particular in repeatedly used frying oils in fast-food and take-away establishments (Claxson *et al.*, 1994). 2,4-Hexadienal has been identified in numerous oxidized glyceridic oils, including canola (low-erucic acid rapeseed), soya bean, cottonseed, sunflower, sesame and palm oils (NTP, 2003).

(i) Fish, seafood and their products

2,4-Hexadienal may occur in seafood, and was detected in biota collected in the United States of America at Lake Pontchartrain (New Orleans, LA) between May and June 1980: in oysters from the mouth of the Inner Harbor Navigation Canal (35 ng/g wet weight) and in clams from the Chef Menteur Pass (7.5 ng/g wet weight). It was not detected in clams from the Rigolets Pass (Ferrario *et al.*, 1985).

In the Republic of Korea, 2,4-hexadienal, (*E*,*E*)- has been identified as a volatile compound in salt-fermented fish paste at concentrations of 491 and 1570 ng/g in anchovy and big-eyed herring pastes, respectively; it was not found in hair tail viscera or shrimp pastes (Cha & Cadwallader, 1995).

Vacuum steam-deodorized fish oils oxidized under fluorescent light (950 lux) at 21 °C were shown to contain 2,4-hexadienal at a concentration of 60 ng/g (Karahadian & Lindsay, 1989).

Venkateshwarlu *et al.* (2004) examined the profiles of volatile compounds in fish oil-enriched milk during cold storage (2 °C) for 14 days, because the development of objectionable, fishy off-flavours is an obstacle in the development of fish oil-enriched foods. 2,4,-Hexadienal, (*E*,*E*)- was detected only on day 14 of storage but not on day 1, 4, 8 or 11.

(ii) Cheese

2,4-Hexadienal was identified as a contributor to the odour of parmesan cheese (Qian & Reineccius, 2002).

(iii) Fruit and vegetables

Takeoka *et al.* (1986) identified 48 volatile compounds in kiwi fruit (*Actinidia chinensis Planch.*); 2,4-hexadienal was identified but represented only 0.01% of total volatile compounds, which constituted 2–10 mg/kg of the fruit pulp.

2,4-Hexadienal was identified as one of the volatile components of tomatoes that increases with high nitrogen and potassium fertilization

(Wright & Harris, 1985), and, according to the authors, may contribute to the undesirable flavour of highly fertilized tomatoes.

(iv) Animal fats

Suzuki & Bailey (1985) quantitated 52 volatile compounds from lamb fat. The average concentration of 2,4-hexadienal was 1.16 mg/kg in clover-fed lamb fat but was less than 0.1 mg/kg in corn-fed lamb fat.

(v) Others

2,4-Hexadienal, (*E*,*E*)- has been detected as a volatile component of piled Toyama Kurocha tea processed in Japan. It was not found in fresh, steamed or fermented tea leaves, but was reported at a concentration of 4 mg/kg in the solar-dried product and at 2 mg/kg in this product after storage for 1 year (Kawakami & Shibamoto, 1991).

Overall, the concentration of 2,4-hexadienal that occurs naturally in fresh vegetal and animal products is generally below 0.3 mg/kg. Higher concentrations (above 1 mg/kg) were observed in lamb fat, in some fish products and in tea. Only qualitative data are available on the concentration of 2,4-hexadienal, (*E*,*E*)- in foods cooked in PUFA-rich culinary oils.

(b) Food additives

In the USA, reported levels of use of 2,4-hexadienal, (*E*,*E*)- range from 0.073 mg/kg in gravies to 2 mg/kg in condiments, relishes and frozen dairy products. Maximum levels of use of up to 6 mg/kg were reported in non-alcoholic beverages. Other reported uses are in alcoholic beverages, soft candy, gelatins and puddings, hard candy, jam and jellies, seasonings and flavourings, snack foods and soups (Burdock, 2005).

Some essential oils that are added to food contain 2,4-hexadienal. One of these is peppermint oil which is used to flavour candies, chewing gums and liqueurs (Mookherjee & Wilson, 2008). In a study conducted in 1988, 2,4-hexadienal was reported to represent 0.1% of the total volatile compounds in the headspace of partially dried, picked peppermint (Mookherjee *et al.*, 1989, cited by Mookherjee & Wilson, 2008).

Kim & Shin (2004) suggested that the essential oil of the beautyberry *Callicarpa japonica Thunb.* could potentially be useful as a modified-atmosphere packing agent to extend the shelf-lives of instant food, because its volatile flavour components, including 2,4-hexadienal, have antibacterial activity against foodborne microorganisms.

Overall, the presence of 2,4-hexadienal in a large number of foods and food products — either naturally or as an additive — suggests that the majority of the population is exposed to this compound. Consumers are also exposed to 2,4-hexadienal in oxidized oils and fats in the diet.

1.3.4 Environmental occurrence

The production and use of 2,4-hexadienal as a food additive and chemical intermediate may result in its release into the environment through various waste streams.

(a) Release

Aldehydes are emitted directly into the atmosphere from a variety of natural and anthropogenic sources and are also formed in situ from the atmospheric degradation of volatile organic compounds (O'Connor *et al.*, 2006). 2,4-Hexadienal was identified in polluted urban air as a product of photo-oxidation of toluene (Dumdei *et al.*, 1988). Unsaturated C6 aldehydes, including 2,4-hexadienal, (*E*,*E*)-, are emitted into the atmosphere from vegetation as a result of leaf wounding (de Gouw *et al.*, 1999; Fall *et al.*, 1999), and have been detected in numerous field studies (König *et al.*, 1995; Helmig *et al.*, 1999; Fukui & Doskey, 2000; O'Connor *et al.*, 2006). 2,4-Hexadienal was tentatively identified as a biogenic volatile organic compound in experiments on 63 vegetal species conducted in 1993

in three specific sites in the USA: Atlanta (GA), near Rhinelander (WI) and near Hayden (CO) (Helmig *et al.*, 1999).

(b) Terrestrial fate

Based on a classification scheme (Swann *et al.*, 1983), an estimated octanol partition coefficient (K_{oc}) value of 17, determined from a structure estimation method (Meylan *et al.*, 1992), indicates that 2,4-hexadienal is expected to be highly mobile in soil. Its potential volatilization from dry soil surfaces may be expected based upon an estimated vapour pressure of 4.8 mm Hg at 25 °C, determined from a fragment constant method (HSDB, 2010).

(c) Aquatic fate

Based on an estimated K_{oc} value of 17, if released into water, 2,4-hexadienal is not expected to adsorb to suspended solids and sediment. Volatilization from water surfaces may be expected based upon a Henry's Law constant of 9.78×10^{-6} atm.m^3/mol (HSDB, 2010).

(d) Atmospheric fate

According to a model of gas/particle partitioning of semi-volatile organic compounds in the atmosphere, 2,4-hexadienal, which has an estimated vapour pressure of 4.8 mm Hg at 25 °C, is expected to exist solely as a vapour. Vapour-phase 2,4-hexadienal is degraded in the atmosphere by a reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 5.9 hours (HSDB, 2010).

2,4-Hexadienal, (*E*,*E*)- was found to undergo rapid isomerization to produce a ketene-type compound (probably *E*-hexa-1,3-dien-1-one). The isomerization process was reversible and formation of the reactant was slightly favoured. Although photolysis appears to be an important atmospheric degradation pathway for 2,4-hexadienal, (*E*,*E*)-, the reversible nature of the photolytic process means that gas-phase reactions with hydroxyl and nitrate radicals are ultimately responsible for the atmospheric removal of these compounds (O'Connor *et al.*, 2006).

(e) Environmental abiotic degradation

2,4-Hexadienal is not expected to undergo hydrolysis in the environment, due to its lack of hydrolysable functional groups, or to photolyse directly due to its lack of absorption in the environmental ultraviolet spectrum (> 290 nm) (HSDB, 2010).

1.3.5 Other occurrence

(a) Indoor air

In the USA, indoor and outdoor air concentrations of 2,4-hexadienal were measured in three houses per county (10 samples of indoor and outdoor air in each). The minimum level of detection was 0.01 μg/m^3. Average indoor and outdoor values, respectively, were: 8.8 μg/m^3 and not detected in Yolo County, 1.1 μg/m^3 and 0.4 μg/m^3 in Los Angeles county, 1.4 μg/m^3 and not detected in Placer County, 1.4 μg/m^3 and 0.4 μg/m^3 in model homes, and 0.5 μg/m^3 and 0.4 μg/m^3 in new homes. 2,4-Hexadienal was not detected in nylon carpet, wood adhesive, latex paint or drywall but was present in particle board (1 ng/g). In five species of lumber used as building material, it was detected at concentrations of 9–22 ng/g of material in 'yellow poplar', Douglas fir and pine, while emissions of 1400 ng/g of material were observed in red oak (Seaman *et al.*, 2007).

(b) Consumer products

Some essential oils that are added to consumer products contain 2,4-hexadienal, in particular peppermint oils used in oral hygiene products (Mookherjee & Wilson, 2008).

(c) Tobacco smoke

2,4-Hexadienal is a component of tobacco leaf and tobacco-smoke volatiles (Florin *et al.*, 1980; Weeks *et al.*, 1989).

(d) Drugs

Extracts of *Callicarpa japonica Thunb.*, which contain 2,4-hexadienal, are reportedly used in traditional medicine (Kim & Shin, 2004).

1.4 Regulations and guidelines

In 1974, 2,4-hexadienal,(E,E)- was given 'Generally Recognized as Safe' status (No. 3429) by the Flavor and Extract Manufacturers' Association (FEMA) (Ford *et al.*, 1988).

2,4-Hexadienal, (*E*,*E*)- is listed in the Toxic Substances Control Act Chemical Substance Inventory of the USA (EPA, 2010). The American Conference of Governmental Industrial Hygienists has not adopted a time-weighted average threshold limit value for this compound (NTP, 2003).

2,4-Hexadienal, (*E*,*E*)- is listed in the register of chemically defined flavourings authorised at national level in the European Union (European Commission, 2011), where its safety evaluation is on-going (EFSA, 2009).

2,4-Hexadienal, (*E*,*E*)- has been listed by the Council of Europe in category B (flavouring substances for which further information is required before the Committee of Experts is able to offer a firm opinion on their safety in use; these substances can be used provisionally in foodstuff) (Council of Europe, 2000). Upper levels of use reported are 0.02 mg/kg in beverages and foods in general, with an exception of 1 mg/kg for candy confectionery (Council of Europe, 2000).

The International Fragrance Association (IFRA, 2009) has recommended that 2,4-hexadienal (CAS No. 80466-34-8 including all geometric isomers) not be used as a fragrance ingredient.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Oral administration

See Table 3.1

3.1.1 Mouse

In a 2-year study, groups of 50 male and 50 female B6C3F$_1$ mice were administered 2,4-hexadienal (89% *trans*,*trans* isomer, 11% *cis*,*trans* isomer) in corn oil by gavage at doses of 0 (controls), 30, 60 or 120 mg/kg body weight (bw) on 5 days a week for up to 105 weeks (Chan *et al.*, 2003; NTP, 2003). The incidence of squamous-cell papilloma and squamous-cell papilloma or carcinoma (combined) of the forestomach showed a positive trend in male and female mice and was significantly increased in high-dose males and mid- and high-dose females. Forestomach squamous-cell carcinomas were observed in high-dose males and females, and the incidence was significantly increased in females; the incidence of squamous-cell carcinoma in the high-dose male and female groups exceeded historical control ranges. Two high-dose males developed a squamous-cell carcinoma of the tongue. Although not significantly increased relative to controls, the incidence exceeded historical control range.

[Tumours of the forestomach and the tongue are rare spontaneous neoplasms in experimental animals.]

Table 3.1 Carcinogenicity studies of oral administration of 2,4-hexadienal by gavage to experimental animals

Species, strain (sex) Duration	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) up to 105 wk	0, 30, 60 or 120 mg/kg bw in corn oil 5 d/wk for 104–105 wk 50/group	Forestomach (squamous-cell papilloma): M[a]–2/50, 4/50, 5/50, 8/50 F[b]–2/50, 2/49, 11/50, 13/50	$P = 0.035$ (high-dose M) $P = 0.022$ (trend M) $P = 0.006$ (mid-dose F) $P < 0.001$ (high-dose F) $P < 0.001$ (trend F)	89% *trans,trans* isomer 11% *cis,trans* isomer
		Forestomach (squamous-cell carcinoma): M[c]–0/50, 1/50, 0/50, 2/50 F[d]–0/50, 0/49, 0/50, 7/50	$P = 0.007$ (high-dose F) $P < 0.001$ (trend F)	
		Forestomach (squamous-cell papilloma or carcinoma combined): M[e]–2/50, 4/50, 5/50, 10/50 F[f]–2/50, 2/49, 11/50, 18/50	$P = 0.009$ (high-dose M) $P = 0.004$ (trend M) $P = 0.006$ (mid-dose F) $P < 0.001$ (high-dose F) $P < 0.001$ (trend F)	
		Tongue (squamous-cell carcinoma): M[g]–0/50, 0/50, 0/50, 2/50	NS	

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) up to 105 wk	0, 22.5, 45, 90 mg/kg bw in corn oil 5 d/wk for 104–105 wk 50/group	Forestomach (squamous-cell papilloma): M[h]–0/50, 3/50, 10/50, 29/50 F[i]–0/50, 1/50, 5/50, 17/50	$P < 0.001$ (mid- and high-dose M, high-dose F) $P = 0.031$ (mid-dose F) $P < 0.001$ (trend M, F)	89% *trans,trans* isomer 11% *cis,trans* isomer
		Forestomach (squamous-cell carcinoma): M–0/50, 0/50, 1/50, 2/50	NS	
		Forestomach (squamous-cell papilloma or carcinoma combined): M[h]–0/50, 3/50, 11/50, 29/50	$P < 0.001$ (mid- and high-dose M) $P < 0.001$ (trend M)	
		Adrenal gland (malignant pheochromocytoma): M[j]–0/50, 1/49, 1/50, 4/49	$P = 0.050$ (high-dose M) $P = 0.014$ (trend M)	

From Chan *et al.* (2003); NTP (2003)

[a] Historical incidence (mean ± SD) for 2-year feed studies in mice: 10/659 (1.8% ± 1.9%), range, 0–6%

[b] Historical incidence (mean ± SD) for 2-year feed studies in mice: 9/659 (1.4% ± 2.0%), range 0–6%

[c] Historical incidence (mean ± SD) for 2-year feed studies in mice: 1/659 (0.2% ± 0.6%), range 0–2%

[d] Historical incidence (mean ± SD) for 2-year feed studies in mice: 1/659 (0.2% ± 0.6%), range 0–2%

[e] Historical incidence (mean ± SD) for 2-year feed studies in mice: 11/659 (2.0% ± 2.0%), range 0–6%

[f] Historical incidence (mean ± SD) for 2-year feed studies in mice: 10/659 (1.6% ± 1.9%), range 0–6%

[g] Historical incidence for 2-year feed studies in mice: 0/659

[h] Historical incidence (mean ± SD) for 2-year feed studies in rats: 2/609 (0.3% ± 0.7%), range 0–2%

[i] Historical incidence for 2-year feed studies in rats: 0/659

[j] Historical incidence (mean ± SD) for 2-year feed studies in rats: 10/607 (1.7% ± 1.4%), range 0–4%

bw, body weight; d, day or days; F, female; M, male; NS, not significant; SD, standard deviation; wk, week or weeks

3.1.2 Rat

In a 2-year study, groups of 50 male and 50 female rats F344/N were administered 2,4-hexadienal (89% *trans*,*trans* isomer, 11% *cis*,*trans* isomer) in corn oil by gavage at doses of 0 (controls), 22.5, 45 or 90 mg/kg bw on 5 days a week for up to 105 weeks (Chan *et al.*, 2003; NTP, 2003). The incidence of squamous-cell papilloma of the forestomach showed a positive trend in males and females, and was significantly increased in the mid- and high-dose groups. The incidence of squamous-cell papilloma in the mid- and high-dose males and females exceeded the historical control range. Squamous-cell carcinomas of the forestomach occurred in one mid- and two high-dose males. Although not significantly increased, the incidence of squamous-cell carcinoma in these groups exceeded the historical control range. The incidence of malignant pheochromocytoma of the adrenal gland was also increased in males.

[Tumours of the forestomach are rare spontaneous neoplasms in experimental animals.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

No studies on the absorption, distribution, metabolism or excretion of 2,4-hexadienal were found in the literature (NTP, 2003). This may be due to the poor stability of the radiolabelled compound and to its rapid reactivity with nucleophiles in blood components. Since aldehyde dehydrogenases (ALDHs) are key enzymes in the metabolism of aldehydes, Picchiottino & Lee (2002) studied their distribution along the gastrointestinal tract of adolescent rats using 2,4-hexadienal as substrate to measure compound-related enzymatic activity. High levels of 2,4-hexadienal-metabolizing ALDH activity were found in the rat forestomach (Picchiottino & Lee, 2002). Administration of 2,4-hexadienal (12.5–200 mg/kg bw) by gavage to young Sprague-Dawley rats for 5 days produced a dose-dependent increase in ALDH activity in the forestomach and oesophagus, but not in the glandular stomach, liver, small intestine or kidney (Lee & Picchiottino, 2003). [This activity may provide partial protection from the direct cytotoxic and genotoxic effects of 2,4-hexadienal after oral administration.]

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

(a) Salmonella reverse mutation assay

2,4-Hexadienal initially gave negative results in a 'spot-test' mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 regardless of the presence of metabolic activation (Florin *et al.*, 1980). However, a clear mutagenic effect of 2,4-hexadienal (in a dose–response manner over 0.1–1.0 µmol) was noted in *S. typhimurium* strain TA104 in a liquid preincubation assay in the absence of metabolic activation (Marnett *et al.*, 1985). Subsequent reports indicated the clear mutagenic activity of 2,4-hexadienal (at 0.01–0.75 µL/plate) in strain TA100 in the presence and absence of metabolic activation using a 30-minute preincubation period (Eder *et al.*, 1992, 1993). As part of a 2-year gavage study, 2,4-hexadienal was tested for the induction of mutations in strains TA98, TA100 and TA1535 strains, and was mutagenic only in

TA100 in the absence of metabolic activation, indicating its role as a direct-acting alkylating agent (Marnett *et al.*, 1985; Eder *et al.*, 1992; NTP, 2003).

(b) Mouse lymphoma cell mutation assay

2,4-Hexadienal induced gene mutations in mouse lymphoma L5178Y cells in the absence of metabolic activation (Seifried *et al.*, 2006).

(c) Micronucleus test

Results on the induction of micronucleated erythrocytes in the bone marrow of male rats and male mice given intraperitoneal injections of acute doses of 2,4-hexadienal were judged to be inconclusive. No increases in micronucleated normochromic erythrocytes were noted in the peripheral blood of male and female mice administered 2,4-hexadienal by gavage for 14 weeks (NTP, 2003).

(d) DNA adducts

Electrophilic α,β-unsaturated aldehydes are considered to be strong direct-acting alkylating agents and are capable of reacting readily with nucleophilic groups of macromolecules such as DNA (Esterbauer, 1985; Eder & Hoffman, 1993; Eder *et al.*, 1993). 2,4-Hexadienal interacted with calf thymus DNA *in vitro* (Frankel *et al.*, 1987) and formed 1,N^2-cyclic-deoxyguanosine and 7,8-cyclic-guanosine adducts in a cell-free system (Eder *et al.*, 1993). After exposure to 2,4-hexadienal, a significant increase in the level of crotonaldehyde–deoxyguanosine-2 adducts in rat forestomach, but not in rat liver or mouse forestomach, was observed by ^{32}P-postlabelling (NTP, 2003). Increased levels of DNA single-strand breaks were noted using the alkaline elution technique in L1210 mouse leukaemia cells treated with subtoxic or slightly toxic doses of 2,4-hexadienal (Eder & Hoffman, 1993). Induction of oxidative DNA damage was investigated in Chinese hamster lung fibroblasts as a consequence of glutathione depletion induced 2,4-hexadienal (Glaab *et al.*, 2001; Janzowski *et al.*, 2003). After 1 hour of incubation in the Comet assay, 100 and 300 µM 2,4-hexadienal caused a 20% depletion in glutathione levels in V79 cells, 300 µM caused extensive oxidative DNA breakage (> 20%) and 100 µM caused weak DNA damage (< 5%) (Janzowski *et al.*, 2003). 2,4-Hexadienal also induced DNA damage in human epithelial colorectal adenocarcinoma cells (Glaab, *et al.*, 2001).

4.3 Mechanistic data

4.3.1 Cytotoxicity

2,4-Hexadienal induced 100% cytotoxicity in murine ascites sarcoma BP8 cells at concentrations of 0.1 and 1.0 mM, and nearly 50% cytotoxicity at 0.01 mM (Pilotti *et al.*, 1975). The cytotoxicity of 2,4-hexadienal has been attributed to a decrease in membrane lipid fluidity (Thelestam *et al.*, 1980; Witz, 1989). A 20% increase in membrane permeability was observed in human lung fibroblasts incubated with 25 mM 2,4-hexadienal for 30 minutes (Thelestam *et al.*, 1980). 2,4-Hexadienal caused a 100% inhibition of non-adrenaline-induced oxidative metabolism in isolated hamster brown fat cells at 1 mM and 20% inhibition at 0.1 mM (Pettersson *et al.*, 1980).

Glutathione *S*-transferases and antioxidant enzymes, such as glutathione, catalase and superoxide dismutase, function as inducible systems against electrophiles to modulate xenobiotic toxicity (Enomoto *et al.*, 2001; Nyska *et al.*, 2001). Nyska *et al.* (2001) found reduced expression of glutathione *S*-transferase-Pi in the foci of basal-cell hyperplasia and in tumour cells in the rat forestomach epithelium after gavage with 2,4-hexadienal, suggesting changes in cellular protection against oxidative or electrophilic DNA damage. Furthermore, the ability of α,β-unsaturated aldehydes to

function as electrophilic DNA-alkylating agents is also enhanced by their inhibitory effect on the DNA repair enzyme, O^6-methylguanine–DNA methyltransferase, which has a cysteine residue in its active site (Krokan *et al.*, 1985; Witz, 1989). Other enzymes inhibited by 2,4-hexadienal include microsomal glucose-6-phosphatase, cytochrome P450 (not specified), aminopyrine demethylase and adenylate cyclase (Jørgensen *et al.*, 1992; NTP, 2003).

Aldo-keto reductase family 1 B10 protein is specifically expressed in the small intestine and colon and may be important in protecting the intestinal epithelium by detoxifying cytotoxic dietary and lipid derived α,β-unsaturated carbonyls, such as 2,4-hexadienal. The reduction of 2,4-hexadienal to its corresponding alcohol by this enzyme had a Michaelis-Menten kinetics value of 96 μM (Zhong *et al.*, 2009).

4.3.2 Cell proliferation

2,4-Hexadienal is cytotoxic and, similarly to other aldehydes, inhibits cell proliferation (Pilotti *et al.*, 1975). In contrast, it also increases the incidence of hyperplasia, squamous-cell papilloma and squamous-cell carcinoma in the forestomach of rats and mice (NTP, 2003).

4.4 Mechanisms of carcinogenesis

Forestomach squamous-cell neoplasms and squamous epithelial hyperplasia (generally recognized as a precursor lesion of neoplasia) developed in rodents administered 2,4-hexadienal by gavage, probably because α,β-unsaturated carbonyls are highly reactive mutagens and carcinogens and tend to be unstable in feed (NTP, 2003). In addition, squamous-cell carcinoma of the oral cavity (tongue) occurred in some male mice, raising the possibility that these rare tumours may be related to exposure to 2,4-hexadienal.

The carcinogenic mechanism is still not clear, but there is convincing evidence that 2,4-hexadienal is a direct-alkylating mutagen in *S. typhimurium* strains TA104 and TA100 (Marnett *et al.*, 1985; NTP, 2003). In addition, 2,4-hexadienal has been shown to interact with calf thymus DNA *in vitro* and to induce DNA strand breaks in mouse leukaemia cells and Chinese hamster lung fibroblasts (Frankel *et al.*, 1987; Eder *et al.*, 1993; Janzowski *et al.*, 2003). These findings imply that highly reactive carbonyl compounds such as 2,4-hexadienal may induce genotoxicity in target tissues by interacting with proteins and enzymes (Esterbauer, 1985; Krokan *et al.*, 1985; Eder *et al.*, 1992). After 14 weeks of exposure to 90 mg/kg 2,4-hexadienal (a dose as high as the high dose used in the 2-year cancer bioassay), crotonaldehyde–deoxyguanosine-2 adduct levels were increased in the rat forestomach (NTP, 2003). Reactive oxygen species, a result of lipid peroxidation during the inflammatory response, can cause accumulation of oxidative DNA damage in forestomach in the form of 8-hydroxydeoxyguanosine. The small increase in chronic inflammation of the forestomach and forestomach ulcers observed in the high-dose group of male rodents only in the 2-year study does not fully support the hypothesis that the cytotoxicity of 2,4-hexadienal was the mechanism that induced dose-related increases in forestomach neoplasms in male and female rats and mice.

There is moderate evidence that tumour induction occurs via a genotoxic mechanism.

5. Summary of Data Reported

5.1 Exposure data

Technical-grade 2,4-hexadienal (80% *trans,trans* isomer, 10–16% *cis,trans* isomer) is prepared by the condensation of acetaldehyde.

2,4-Hexadienal occurs in many foods, and levels increase during cooking as a result of

auto-oxidation of polyunsaturated fatty acids of plant and animal origin. 2,4-Hexadienal is also added to food as a flavouring ingredient. It is used as an intermediate in the production of 3,5,7-nonatrien-2-one, sorbic acid, polymethine dyes, mitomycins and antihypercholesteremics. Occupational exposure to 2,4-hexadienal may occur during its production and use.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2,4-Hexadienal was tested for carcinogenicity by oral administration by gavage to mice and rats. In mice, it increased the incidence of forestomach squamous-cell papilloma and carcinoma in females, squamous-cell papilloma or carcinoma (combined) in males and females, and squamous-cell carcinoma of the tongue in males. In rats, oral administration of 2,4-hexadienal caused an increase in the incidence of forestomach squamous-cell papilloma in males and females, forestomach squamous-cell papilloma or carcinoma (combined) in males, and malignant pheochromocytoma of the adrenal gland in males.

Tumours of the forestomach and the tongue are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

No toxicokinetic data were available to the Working Group.

2,4-Hexadienal is a direct-acting alkylating agent that forms DNA adducts both *in vivo* and *in vitro*, causes glutathione depletion and DNA strand breaks, and is mutagenic in bacteria.

A small increase in chronic inflammation of the forestomach in male rats and in forestomach ulcers in male mice was observed only in the high-dose groups in the cancer bioassay. This does not fully support the hypothesis that cytotoxicity was the mechanism that induced the dose-related increases in forestomach neoplasms in male and female rats and mice. The relevance of the tumour response in experimental animals to humans cannot be excluded.

There is moderate evidence that tumour induction occurs via a genotoxic mechanism.

The mechanistic data provide some additional support for the relevance of the animal carcinogenicity data to humans.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,4-hexadienal.

6.3 Overall evaluation

2,4-Hexadienal is *possibly carcinogenic to humans (Group 2B).*

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