OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Proposition 65

Evidence on the Carcinogenicity of Vinyl Acetate

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Reproductive and Cancer Hazard Assessment Branch
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CONTRIBUTORS

The Office of Environmental Health Hazard Assessment's (OEHHA) Cancer Toxicology and Epidemiology Section within the Reproductive and Cancer Hazard Assessment Branch was responsible for the preparation of this document.

Authors (listed alphabetically by last name)

Vanessa Cheng, Ph.D.
Associate Toxicologist

Sarah Elmore, Ph.D.
Staff Toxicologist

Neela Guha, Ph.D., M.P.H.
Research Scientist III

Kate Li, Ph.D., DABT
Staff Toxicologist

Gwendolyn Osborne, M.D., M.P.H.
Staff Toxicologist

Karin Ricker, Ph.D.
Staff Toxicologist

Feng C. Tsai, Ph.D., M.S.
Staff Toxicologist

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Internal OEHHA Reviewers

Meng Sun, Ph.D., M.S.
Chief, Cancer Toxicology and Epidemiology Section

Martha S. Sandy, Ph.D., M.P.H.
Chief, Reproductive and Cancer Hazard Assessment Branch

Kannan Krishnan, Ph.D.
Assistant Deputy Director, Division of Scientific Programs

Acting Director

David Edwards, Ph.D.

PREFACE

This document presents evidence relevant to the evaluation of the carcinogenicity of vinyl acetate.

Proposition 65[1] requires the publication of a list of chemicals known to the state to cause cancer or reproductive toxicity within the meaning of the Act (Health and Safety Code section 25249.8). The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency maintains this list in its role as the lead agency for implementing Proposition 65. The Carcinogen Identification Committee (CIC) advises and assists OEHHA and adds chemicals to the Proposition 65 list of chemicals that cause cancer, as required by Health and Safety Code section 25249.8.

The CIC serves as the state's qualified experts for determining whether a chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer within the meaning of the Act (Health and Safety Code section 25249.8.). The CIC also provides advice and consultation regarding which chemicals should receive their review. At their meeting in November 2016, the CIC recommended that vinyl acetate be placed in the 'medium' priority group for future listing consideration. OEHHA selected vinyl acetate for consideration for listing by the CIC, and in August 2023 OEHHA solicited from the public information relevant to the assessment of the evidence on its carcinogenicity. OEHHA reviewed and considered the information received in preparing this document.

The CIC is scheduled to meet on December 19, 2024. OEHHA is providing this document to the CIC to assist the Committee in its deliberations on whether or not vinyl acetate should be listed under Proposition 65 for the cancer endpoint. The original papers and reports discussed in this document are provided to the CIC.

OEHHA is holding a public comment period on this hazard identification document. For information on how to comment go to https://oehha.ca.gov/comments. Comments on this document will be included in the hazard identification materials that are provided to the CIC members prior to the meeting.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (California Health and Safety Code 25249.5 *et seq*.)

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LIST OF ABBREVIATIONS

Abbreviation	Full name
95% CI	95% Confidence Interval
β	Regression coefficient
γ-H2AX	H2A histone family member X phosphorylated on serine 139
µg	Micrograms
µm	Micrometers
µM	Micromolar
AhR	Aryl hydrocarbon receptor
ALDH	Aldehyde dehydrogenase
AO	Aldehyde oxidase
ASPEN	Assessment System for Population Exposure Nationwide
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body mass index
BNPP	*Bis* (p-nitrophenyl) phosphate
BrdU	5-bromo-2'-deoxyuridine
BW	Body weight
CA	Chromosomal aberrations
CES	Carboxylesterase
CHO	Chinese hamster ovary
CI	Confidence interval
CIC	Carcinogen Identification Committee
CoA	Coenzyme A
CRL	Charles River Laboratories
CYP	Cytochrome P450
dA	Deoxyadenosine
dC	Deoxycytidine
dG	Deoxyguanosine
DNA	Deoxyribonucleic acid
DPXL	DNA-protein crosslink
ECHA	European Chemical Agency
EPL	Environmental Pathology Laboratories, Incorporated
ER	Estrogen receptor
EVA	Ethylene-vinyl acetate

Abbreviation	Full name
F	Female
F_0	Parental generation
F_1	First filial generation
F344	Fischer 344
FBS	Fetal bovine serum
g/mol	Grams per mole
g/kg	Grams per kilogram
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GD	Gestation day
GI	Gastrointestinal
GSH	Glutathione, reduced form
Gy	Gray, unit of ionizing radiation
HAWC	Health Assessment Workspace Collaborative
HIC	Highest ineffective concentration
HID	Highest ineffective dose
HPLC	High-performance liquid chromatography
HPRT	Hypoxanthine-guanine phosphoribosyl transferase
hr	hours
HR	Hazard ratio
HS	Horse serum
i.p.	Intraperitoneal
IARC	International Agency for Research on Cancer
IQR	Interquartile range
JBRC	Japan Bioassay Research Center
KCs	Key characteristics
kg	Kilogram
Km	Michaelis constant
Kow	Octanol-water partition coefficient
LC	Liquid chromatography
LC-MS	Liquid chromatography coupled with mass spectrometry
LEC	Lowest effective concentration
LED	Lowest effective dose
M	Male
mCi	Millicurie

Abbreviation	Full name
mg	Milligram
mg/kg	Milligrams per kilogram
mg/kg-day	Milligrams per kilogram per day
mg/l	Milligrams per liter
mg/m^2	Milligrams per square meter
mg/m^3	Milligrams per cubic meter
Min	Minute
mM	Millimolar
mmHg	Millimeters of mercury
MN	Micronuclei
mol/l	Moles per liter
MS	Mass spectrometry
N2-Etd-dG	N2-ethylidene-2'-deoxyguanosine or N2-ethylidene-dG
N2-Ethyl-dG	N2-ethyl-2'-deoxyguanosine
NATA	National Air Toxics Assessment
NCI	National Cancer Institute
NIOSH	National Institute of Occupational Safety and Health
NOx	Nitrogen oxides
NR	Not reported
NTP	National Toxicology Program
^oC	Degrees Celsius
OEHHA	Office of Environmental Health Hazard Assessment
OR	Odds ratio
PBMC	Peripheral blood mononuclear cell
PPAR	Peroxisome proliferator-activated receptor
ppm	Parts per million
PR	Progesterone receptor
PVA	Polyvinyl acetate
R	Rare
r^2	Correlation coefficient
ROS	Reactive oxygen species
SCC	Squamous cell carcinoma
SCE	Sister chromatid exchange
SCP	Squamous cell papilloma

Abbreviation	Full name
SD rats	Sprague-Dawley rats
SE	Standard error
SES	Socioeconomic status
SOD	Superoxide dismutase
SWIFT AS	Sciome Workbench for Interactive Computer-Facilitated Text-mining Active Screener
TK	Thymidine kinase
UCC	Union Carbide Corporation
UDS	Unscheduled DNA synthesis
UK	United Kingdom
US	United States
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
VAM	Vinyl acetate monomer
Vmax	Maximum velocity of an enzymatic reaction
v/v	(Concentration) by volume
XO	Xanthine oxidase

SUMMARY

This document presents evidence relevant to the evaluation of the cancer hazard of vinyl acetate. Vinyl acetate was placed in the “medium” priority group for future listing consideration by the Carcinogen Identification Committee (CIC) at their 2016 meeting. The International Agency for Research on Cancer (IARC) classified vinyl acetate as possibly carcinogenic to humans (Group 2B carcinogen) in 1995. In 2011, the European Chemical Agency classified vinyl acetate as a Category 2 carcinogen, suspected of causing cancer.

Vinyl acetate is a synthetic chemical with a high production volume used in many industrial and commercial applications. It is used mainly as a monomer in the production of polymers and copolymers, such as polyvinyl acetate, polyvinyl alcohol, and ethylene-vinyl acetate copolymers. Vinyl acetate-based polymers are used in adhesives and glues, paints, paper coatings, textile and leather finishing, plastics and resins, inks and lacquers, heat sealing films, pesticides, and cosmetics. Vinyl acetate is also approved as a food additive (as a modifier for food starch), while vinyl acetate-based polymers (e.g., vinyl acetate-vinyl laurate copolymers) have been approved as food additives for use in chewing gum bases. Vinyl acetate has been detected in air, cigarette smoke, microwave-heat-susceptor food packaging, carpet, building materials, water, soil, and sediment. The general population may be exposed to low levels via inhalation of contaminated air, ingestion of contaminated food or water, or dermal contact with products containing residual vinyl acetate monomer.

Systematic Literature Review Approach

Using a systematic approach similar to that used by the National Toxicology Program (NTP) for its Report on Carcinogens (RoC) (NTP 2015), the Office of Environmental Health Hazard Assessment (OEHHA) conducted literature searches on the carcinogenicity of vinyl acetate (last comprehensive search, May 2023). The literature searches included primary searches in major biomedical databases, searches in other data sources such as reports by other health agencies, and additional focused searches. The literature searches were supplemented with a public data call-in period from July 7 to September 18, 2023. An overview of the systematic literature review approach is presented in Section 2, and more detailed information can be found in Appendix A.

Carcinogenicity Studies in Humans

The few epidemiological studies on vinyl acetate reported results from one study population per cancer outcome: breast cancer, lymphohematopoietic cancer, brain cancer, lung cancer and angiosarcoma of the liver. One study that assessed the association between vinyl acetate in residential ambient air and breast cancer in women in the greater Los Angeles region reported increased risk estimates after adjustment for multiple potential confounders and in a number of stratified analyses. The rest of the studies were in workers with potentially high exposures to vinyl acetate without further information on intensity, frequency, or duration of exposure, and with co-exposures to vinyl chloride and/or other carcinogens. Although some of these occupational studies noted increased risks associated with vinyl acetate, limitations included one or more of the following: small numbers of exposed cases, imprecise confidence intervals or reporting, crude methods for reporting exposure to vinyl acetate (e.g. 'ever exposure'), and no accounting for co-exposures in the workplace in the statistical analysis.

Carcinogenicity Studies in Animals

Carcinogenicity studies of vinyl acetate have been conducted in male and female Sprague-Dawley (SD) rats, SD derived Crl:CD(SD)BR rats, Fischer 344 rats, F344/DuCrj rats, Wistar rats, Swiss mice, Swiss derived Crl:CD-1(ICR)BR mice, and Crj:BDF1 mice.

Statistically significant tumor findings were observed in multiple studies in both rats and mice. Some of the tumors observed in these studies occurred in tissues distant to the point of entry and were not part of the gastrointestinal or respiratory tract (e.g., tumors of the uterus, thyroid gland, pancreas, and adrenal glands in drinking water studies in rats, Table 11 and Tables 13–17). Some of the tumors observed occurred in multiple dose groups, with significant dose-related trends (e.g., rare forestomach squamous cell carcinomas in male and female F_1 Sprague-Dawley rats, Table 14 and Table 15; forestomach acanthoma in male F_1 Swiss mice, Table 24). Some tumors were significantly increased at the low- or mid-dose but not the high-dose (e.g., thyroid gland C-cell tumors in female F344/DuCrj rats, Table 13; adrenal gland pheochromoblastoma in female F_1 Sprague-Dawley rats, Table 15; malignant lymphoma of the spleen in female Crj:BDF1 mice, Table 22). Statistically significant tumor findings[2] are as follows, with many of the same tumor types seen in multiple studies:

[2] Many of the statistically significant tumor findings were also rare tumors. For example, nasal cavity tumors in male and female Crl:CD(SD)BR rats, oral cavity tumors in male and female F344/DuCrj rats, forestomach squamous cell carcinomas in male and female SD rats, and many of the upper gastrointestinal tract tumors in male and female Crj:BDF1 mice. See Section 4 and Table 26 for detailed information.

- Respiratory system:
    - Nasal tumors (squamous cell papilloma alone, or squamous cell papilloma, carcinoma and carcinoma *in situ* combined)
        - Male Crl:CD(SD)BR rats
    - Nasal squamous cell carcinoma
        - Female Crl:CD(SD)BR rats
    - Pharynx carcinoma
        - Male Wistar rats
    - Lung adenoma
        - Female Swiss mice
- Digestive system:
    - Oral cavity squamous cell tumors (carcinoma, or papilloma and carcinoma combined)
        - Male and female Swiss mice
    - Oral cavity and lip squamous cell carcinoma
        - Male and female F344/DuCrj rats
        - Male and female SD rats
        - Male and female Wistar rats
        - Male and female Crj:BDF1 mice
    - Tongue squamous cell carcinoma
        - Female Wistar rats
        - Male and female Swiss mice
    - Esophagus squamous cell carcinoma
        - Male and female Wistar rats
        - Male Crj:BDF1 mice
        - Male and female Swiss mice
    - Esophagus acanthoma
        - Female Swiss mice
    - Forestomach squamous cell carcinoma
        - Male and female SD rats
        - Male and female Wistar rats
        - Male and female Crj:BDF1 mice
        - Female Swiss mice
    - Forestomach acanthoma
        - Male and female Swiss mice
    - Liver hepatocellular adenoma
        - Female Fischer 344 rats
    - Pancreatic islet cell adenoma
        - Male SD rats
    - Pancreatic exocrine adenoma
        - Male SD rats
        - Male Wistar rats
- Endocrine system:

    - Pituitary adenoma
        - Female Fischer 344 rats
    - Thyroid C-cell tumors (adenoma and carcinoma combined)
        - Female Fischer 344 rats
        - Female F344/DuCrj rats
    - Adrenal gland pheochromoblastoma
        - Female SD rats
        - Male Wistar rats
    - Adrenal gland pheochromocytoma
        - Female Wistar rats
- Reproductive system:
    - Uterine adenocarcinoma
        - Female Fischer 344 rats
        - Female Wistar rats
    - Uterine endometrial stromal polyps
        - Female Fischer 344 rats
    - Uterine leiomyosarcoma
        - Female Swiss mice
    - Uterine fibrosarcoma
        - Female Wistar rats
    - Testicular interstitial cell tumors
        - Male Fischer 344/DuCrj rats
- Immune system:
    - Lymphomas and leukemias of the hemolymphoreticular tissues
        - Female Wistar rats
    - Malignant lymphoma of the spleen
        - Female Crj:BDF1 mice
- Auditory system:
    - Zymbal gland carcinoma
        - Female Swiss mice
- Integumentary system:
    - Mammary adenocarcinoma
        - Female Fischer 344/DuCrj rats
    - Mammary liposarcoma
        - Female Swiss mice

In addition, the following rare tumors were observed but did not reach statistical significance.

- Nasal cavity squamous cell carcinoma in male Crl:CD(SD)BR rats
- Nasal cavity carcinoma *in situ* in male Crl:CD(SD)BR rats
- Oral cavity and lip squamous cell papilloma in male F344/DuCrj rats
- Tongue squamous cell carcinoma in female SD rats
- Larynx squamous cell carcinoma in female Crl:CD(SD)BR rats

- Larynx squamous cell papilloma in male Crj:BDF1 mice
- Forestomach squamous cell papilloma in female Crj:BDF1 mice

The vinyl acetate metabolite acetaldehyde is classified as a “Group 2B” carcinogen (possibly carcinogenic to humans) by IARC (IARC 1987; 1999) and as “Reasonably anticipated to be a human carcinogen” by the NTP’s RoC (NTP 2021).[3] Both classifications are based on sufficient evidence of carcinogenicity in experimental animals. For a summary of the tumors induced by acetaldehyde, see Section 4.3.2.

Mechanistic Considerations and Other Relevant Data

Pharmacokinetics and metabolism

The pharmacokinetics and metabolism of vinyl acetate have been studied in humans and animals *in vivo* and *in vitro*, and in cell-free systems. Vinyl acetate is quickly absorbed and distributed throughout the body, with its excretion largely completed within 24 hours via expired air, urine and feces.

In an initial reaction, vinyl acetate is hydrolyzed by carboxylesterases (CES) to form acetic acid and vinyl alcohol, the latter of which quickly rearranges to acetaldehyde, a known genotoxic carcinogen. Acetaldehyde is metabolized by aldehyde dehydrogenases (ALDHs; primarily ALDH2) to acetic acid, which in turn is further metabolized in the tricarboxylic acid (Krebs) cycle.

In other metabolic reactions, vinyl acetate can be conjugated with reduced glutathione (GSH). Downstream of vinyl acetate, acetaldehyde can also be metabolized by cytochrome P450 (CYP) enzymes, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), xanthine oxidase (XO), or aldehyde oxidase (AO). Metabolic reactions with CYP enzymes and GAPDH likely play no significant role under normal physiological conditions. Oxidation of acetaldehyde via XO and AO produces reactive oxygen species (ROS) *in vitro* and in cell free systems; production of alkyl radicals has been reported via XO catalyzed oxidation *in vivo* and *in vitro*.

ALDH2 plays a key role in detoxifying acetaldehyde. Genetic polymorphisms of ALDH2 can result in a partial or complete loss of function of this enzyme, resulting in increased levels of vinyl acetate-derived acetaldehyde, which in turn increases the formation of ROS, carbon-centered radicals, DNA and/or protein adducts, and DNA-protein crosslinks (DPXLs).

[3] Vinyl acetate itself was classified by IARC (1995) as a Group 2B carcinogen and has not been reviewed and classified by NTP RoC or other US health agencies. See Section 1.4 for details.

Key characteristics of carcinogens

The key characteristics (KCs) of carcinogens are characteristics of agents that cause cancer in humans and can encompass many types of mechanistic endpoints. OEHHA used the KCs of carcinogens to systematically identify, organize, and summarize mechanistic information from studies of vinyl acetate. Evidence related to three of the 10 KCs was identified for vinyl acetate, and this evidence is briefly summarized here. See Section 5.2 for more detailed summaries of the data relevant to these KCs. Overall, mechanistic data support the observations that vinyl acetate can be metabolically activated to an electrophilic chemical (acetaldehyde) and form DNA adducts, causes genotoxicity including clastogenicity and DNA damage, and induces cell proliferation and pre-neoplastic lesions such as hyperplasia and dysplasia.

KC1. Is electrophilic or can be metabolically activated

Vinyl acetate is metabolized to acetaldehyde, which is electrophilic and has been shown to bind to DNA in studies in rodents *in vivo*, human and other mammalian cells *in vitro*, and in cell-free systems. Moreover, two recent *in vivo* studies of vinyl acetate conducted in rats have demonstrated that administration of [$^{13}C_2$]-vinyl acetate via inhalation results in the formation of DNA adducts in the nasal respiratory and olfactory epithelia, and in peripheral blood mononuclear cells.

KC2. Is genotoxic

Vinyl acetate and its metabolite acetaldehyde have long been recognized as genotoxic. IARC concluded in 1995 that both “vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*.” Overall, there are many studies reporting chromosomal effects of vinyl acetate, and a few studies reporting DNA damage and mutagenicity associated with exposure to vinyl acetate.

A number of *in vitro* studies in human cells and *in vivo* studies in rodents have reported increases in chromosomal effects following treatment with vinyl acetate, including increases in micronuclei formation, chromosomal aberrations (CAs), and sister chromatid exchange (SCE). In addition, one *in vitro* study of vinyl acetate in animal cells reported an increase in SCE, while a small study in exposed humans, published in Russian, reported increased levels of CAs in the lymphocytes of polyvinyl acetate manufacturing workers.

A few studies have reported that vinyl acetate induced DNA damage. As discussed under KC1, two studies reported the formation of DNA adducts in rats *in vivo*, following administration of radiolabeled vinyl acetate. In addition, increases in DNA crosslinks were observed in a study of human cells *in vitro,* a study of rodent cells *in vitro*, and an acellular system following treatment with vinyl acetate.

Vinyl acetate induced mutations at the thymidine kinase *(TK)* locus in human TK6 lymphoblastoid cells *in vitro* and in a mouse lymphoma cell line. However, vinyl acetate did not induce mutations in bacteria, or at the *HPRT* locus in human TK6 cells.

As observed in *in vitro* studies, vinyl acetate is genotoxic at non-cytotoxic concentrations (Table 30). The genotoxicity findings for vinyl acetate are consistent with and supported by those seen in studies of its metabolite, acetaldehyde.

KC10. Alters cell proliferation, cell death or nutrient supply

Vinyl acetate has been shown to increase cellular proliferation, hyperplasia, or dysplasia in rodents. These effects were observed in both inhalation and oral exposure studies and findings were predominantly observed in the upper respiratory and digestive tracts (e.g., nose, oral cavity, esophagus, forestomach, trachea). In male rats, increased cell proliferation was observed in the nasal respiratory and olfactory epithelia after a single inhalation exposure, and in the nasal olfactory epithelium after 20 repeated exposures. Cell proliferation of the oral cavity was increased in rats and mice exposed to vinyl acetate via drinking water for 92 days. Tissue concordance between tumors and hyperplasia/dysplasia was observed for several sites in some long-term cancer bioassays of vinyl acetate. For example, in female rats, hyperplasia and tumors were observed in the nasal cavity, esophagus, and thyroid tissues. In male mice, dysplasia and tumors were observed in the esophagus in one set of studies, and in another study hyperplasia and tumors were observed in the oral cavity and the esophagus. Finally, in female mice, hyperplasia and tumors were observed in the oral cavity and forestomach.

Similarities between Vinyl Acetate and Its Metabolite Acetaldehyde: Carcinogenicity and Genotoxicity

IARC reviewed vinyl acetate in 1995 and classified it as a Group 2B carcinogen (IARC 1995). IARC's classification for vinyl acetate is based on the following considerations, as noted in the "Overall evaluation" section of the monograph:

> "Vinyl acetate is possibly carcinogenic to humans (Group 2B). In making the overall evaluation, the Working Group took into account the following evidence:
>
> (i) Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues.
>
> (ii) There is sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde (IARC 1987). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation.

(iii) Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*."Table 31 in Section 6 shows the similarities of the tumor sites/types and

genotoxicity endpoints between vinyl acetate and acetaldehyde. Briefly, there is evidence that vinyl acetate and acetaldehyde both cause:

- Tumors in rats
    - Nasal tumors (route: inhalation)
    - Hemolymphoreticular cancer (leukemia and lymphoma combined) (route: drinking water)
    - Pancreatic tumors (islet cell adenoma) (route: drinking water)
    - Mammary gland tumors (route: drinking water)
- Genotoxicity
    - Chromosomal effects
        - Micronuclei formation in human cells *in vitro* and rodents *in vivo*
        - Chromosomal aberrations in human cells *in vitro* and rodents *in vivo*
        - Sister chromatid exchange in human and animal cells *in vitro* and rodents *in vivo*
    - DNA damage
        - Formation of the same type of DNA adducts in rats *in vivo* (e.g., N2-Ethyl-dG, N2-propano-dG)
        - DNA-protein crosslinks in human and rodent cells *in vitro* and in an acellular system
    - Mutagenicity
        - Mutations at *thymidine kinase* locus in human and mouse cells *in vitro*
        - No mutations in *S. typhimurium*

1. INTRODUCTION

1.1 Chemical Identity of Vinyl Acetate

Vinyl acetate is a monocarboxylic unsaturated aliphatic ester (Figure 1). At room temperature, vinyl acetate is a colorless volatile liquid with a sweet odor. It is soluble in water and most organic solvents (e.g., acetone) (IARC 1995). With its low octanol-water coefficient, vinyl acetate is unlikely to bioconcentrate in the food chain. Selected chemical properties are listed in Table 1.

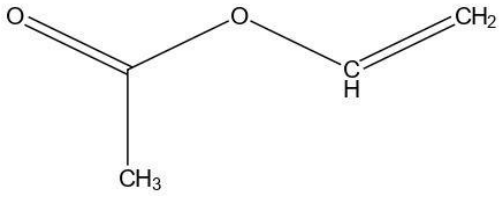

Figure 1. Chemical structure of vinyl acetate

Table 1. Selected chemical properties of vinyl acetate

Chemical name	Vinyl acetate
Synonyms	Acetic acid ethenyl ester; Ethenyl acetate
Chemical Abstracts Service Registry Number	108-05-4
Molecular formula	$C_4H_6O_2$
Molecular weight (g/mol)	86.09
Boiling point (ºC)	72.3
Melting point (ºC)	-96.6
Vapor pressure (mmHg)	90.2
Water solubility (mol/L)	0.232
Octanol-water coefficient (Log K_{ow})	0.73

Values are from US EPA's CompTox Chemical Dashboard (https://comptox.epa.gov/dashboard/chemical/details/DTXSID3021431; accessed November 14, 2023).

1.2 Production, Sources, and Use

Vinyl acetate is a synthetic chemical with a high production volume used in many industrial and commercial applications. It is used mainly as a monomer in the production of polymers and copolymers, including polyvinyl acetate (PVA), polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate (EVA) copolymers, and polyvinyl chloride-acetate copolymers (IARC 1995; US EPA 2020). These vinyl acetate-based polymers are used in adhesives (as an adhesion/cohesion promoter) and glues, paints, paper coatings, textile and leather finishing, plastics and resins, inks and lacquers, heat sealing films, pesticides, and cosmetics (e.g., in hairspray) (ATSDR 2023; Carthew et al. 2002; IARC 1995; US EPA 2020). Vinyl acetate is also approved as a food additive (as a modifier for food starch (US FDA 2023)), while vinyl acetate-based polymers (e.g., PVA and vinyl acetate-vinyl laurate copolymers) have been approved as food additives for use in chewing gum bases, with allowable residual levels of vinyl acetate to be less than 5 ppm (US FDA 2015, 2019, 2023).

1.3 Occurrence and Exposure

Vinyl acetate has been detected in air (e.g., ambient air near emission sources), water (surface water, groundwater, and wastewater effluents), soil, and sediment (ATSDR 2023; IARC 1995; Rago et al. 2021).

Vinyl acetate was detected at levels less than 1 ppm in vinyl acetate-vinyl laurate copolymers intended for use as a chewing gum base (US FDA 2019).

Vinyl acetate has also been detected in:

- Cigarette smoke (estimated emissions: 0.1-4.0 µg vinyl acetate per cigarette) (Coggins et al. 2013; Diekmann et al. 2002; Xu et al. 2017) and cigar smoke (no concentrations given) (Cheng et al. 2022). The presence is due to the use of PVA or EVA as an adhesive in cigarette paper (Coggins et al. 2013; Xu et al. 2017).
- Microwave-heat-susceptor food packaging (estimated emissions: 0.01-0.88 µg/inch^2 during microwave cooking) (McNeal and Hollifield 1993)
- Carpets (estimated emissions: 38.6 mg/m^2 over the first 24 hours, and 85.3 mg/m^2 over 168 hours) (Hodgson et al. 1993)
- Building materials (0.1-2.6% mass fraction as performance enhancer in flooring or gypsum wallboards, also detected in polyurethane foam insulation, and glass or mineral fiber insulation) (Huang et al. 2022)
- Nail polish products (203 µg/ml; detected in one out of 156 products tested) (DTSC 2023)

Occupational exposure to vinyl acetate may occur during the production, transport or use of vinyl acetate monomers or vinyl acetate-based polymers via inhalation or dermal contact (ATSDR 2023; IARC 1995). In the workplace, vinyl acetate has been detected in the air at a vinyl acetate manufacturing plant (Deese and Joyner 1969) and at a carpet manufacturing facility using PVA-based glues (Khoshakhlagh et al. 2023). No data on general population exposures from the uses of vinyl acetate-based polymers are available. According to ATSDR (2023), the general population may be exposed to low levels via:

- Inhalation of contaminated air (e.g., cigarette smoke or vapor intrusion from contaminated soil)
- Dermal contact from products containing residual vinyl acetate monomers (e.g., use of paints)
- Ingestion of contaminated water or food (e.g., vinyl acetate migration from food packaging or residue in food additives)

1.4 Review by Other Health Agencies

The International Agency for Research on Cancer (IARC) reviewed vinyl acetate in 1995 and classified it as a Group 2B carcinogen (IARC 1995). IARC's classification for vinyl acetate is based on the following considerations, as noted in the "Overall evaluation" section of the monograph:

> "Vinyl acetate is possibly carcinogenic to humans (Group 2B). In making the overall evaluation, the Working Group took into account the following evidence:
>
> (i) Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues.
>
> (ii) There is sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde (IARC 1987). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation.
>
> (iii) Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*."

Vinyl acetate has not been reviewed or classified as to its potential carcinogenicity by the US Environmental Protection Agency (US EPA), the National Institute for Occupational Safety and Health (NIOSH), the National Toxicology Program (NTP) Report on Carcinogens (RoC), or the US Food and Drug Administration (US FDA).

In 2011, the European Chemical Agency (ECHA 2011) reviewed the carcinogenicity of vinyl acetate and classified it as a Category 2 carcinogen – suspected of causing cancer.

2. OVERVIEW OF SYSTEMATIC LITERATURE REVIEW APPROACH

2.1 Literature Search Process

Literature searches on the carcinogenicity of vinyl acetate were conducted mainly in May 2023. The goal was to identify peer-reviewed journal articles, print and digital books, reports, and gray literature that potentially reported toxicological and epidemiologic information on the carcinogenicity of this chemical.

As described below, we used an approach similar to that recommended by the National Toxicology Program (NTP) Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2015).

The searches were conducted using the following three approaches:

- Primary searches in major biomedical databases, conducted by OEHHA librarian Nancy Firchow, MLS.
- Searches in other data sources, including authoritative reviews and reports, and databases or web resources, conducted by OEHHA scientists and the OEHHA librarian.
- Additional focused searches, conducted by OEHHA scientists.

In addition to information identified from these searches, OEHHA also considered the following:

- Submissions received during the data call-in period (July 7 – September 18, 2023) (https://oehha.ca.gov/proposition-65/crnr/request-relevant-information-carcinogenicity-vinyl-acetate)

Primary searches for vinyl acetate were executed using chemical synonyms in combination with search terms for human cancer studies, animal cancer studies, toxicokinetic studies, and mechanistic studies for genotoxicity and other key characteristics. There were no restrictions in the searches on exposure route or duration of exposure on cancer studies in humans, cancer studies in animals or mechanistic studies, or on publication language.

For detailed information on the literature search process, please see Appendix A.

2.2 Literature Screening Process

Process for human cancer studies, animal cancer studies, and studies on key characteristics of carcinogens and other mechanistic concepts

HAWC (Health Assessment Workspace Collaborative, https://hawcproject.org) (Shapiro et al. 2018) was used as a tool to screen and tag the literature. First, citations retrieved from the literature searches were uploaded to EndNote libraries, and duplicates were removed. Next, these EndNote libraries were uploaded to HAWC for multi-level screening using specific inclusion and exclusion criteria (see Appendix A).

In Level 1 screening in HAWC, each citation was first screened by at least one OEHHA scientist, based solely on titles and abstracts, to eliminate studies or articles that do not contain information on vinyl acetate on any of the key topics covered in this cancer hazard identification document, such as cancer studies in humans and animals, toxicokinetics, metabolism, genotoxicity, or other cancer-associated mechanisms. The Level 1 screen was intended to identify all studies deemed to have a reasonable possibility of containing information that could be useful for the review process. Papers identified for inclusion during Level 1 screening were tagged in HAWC according to key topics.

In Level 2 screening, full-text papers for all citations that passed the Level 1 screening were obtained and screened by at least one OEHHA scientist, using similar inclusion/exclusion criteria as was used in the Level 1 screening.

Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC. Level 1 and 2 screenings were conducted and HAWC search results were updated if additional relevant studies in addition to those cited in the original set of publications (“secondary citations”) were identified.

Table Builder (Shapiro et al. 2018), a web-based application, was applied to systematically extract and analyze the data that were included in Section 3, Carcinogenicity studies in humans. Additionally, Table Builder was used as a custom-made database to generate Word tables in this document.

Process for vinyl acetate pharmacokinetics and metabolism-related studies

Five Endnote libraries were created and compiled in May 2023 (https://www.sciome.com/swift-activescreener/). The five libraries each focused on a specific topic: vinyl acetate absorption, distribution, metabolism and elimination (ADME), acetaldehyde metabolism, vinyl acetate and acetaldehyde studies, acetaldehyde and CYP450 or monooxygenase studies, and enzyme polymorphisms. Two libraries (vinyl

acetate and acetaldehyde studies, acetaldehyde and CYP450 or monooxygenase studies) were small and were screened manually by two OEHHA scientists.

Sciome Workbench for Interactive computer-Facilitated Text-mining Active Screener (SWIFT AS) (Howard et al. 2020) was used as a tool to facilitate the initial screening of the remaining three libraries related to pharmacokinetics and metabolism, namely vinyl acetate ADME, acetaldehyde metabolism, and enzyme polymorphisms. This initial screening in SWIFT AS allowed for efficient initial literature inclusion and exclusion with the help of artificial intelligence. In each project, two OEHHA scientists independently completed the screening for a decision to be made on each title and abstract, following predefined inclusion and exclusion criteria.

Total references

More than 1700 references[4], including peer-reviewed journal articles and government reports, were identified for inclusion through these search strategies. Among these, over 170 references were cited in this document.

[4] Among these, more than 1100 focus on genetic polymorphisms of ALDH2, a key enzyme in vinyl acetate (and acetaldehyde) metabolism.

3. CARCINOGENICITY STUDIES IN HUMANS

There were few epidemiological studies that reported on cancer associated with exposure to vinyl acetate. One study assessed residential exposure to vinyl acetate in ambient air, while the rest of the studies were in workers. The outcomes studied were lymphohematopoietic cancer (Ott et al. 1989; Union Carbide 1989), brain cancer (Austin and Schnatter 1983; Leffingwell et al. 1983), lung cancer (Waxweiler et al. 1981), angiosarcoma of the liver (Lewis and Rempala 2003; Waxweiler 1981), and breast cancer (Heck et al. 2024). Two studies did not report risk estimates nor enough data for their calculation (Waxweiler 1981; Waxweiler et al. 1981). The publication by Waxweiler (1981) was excluded from further review because the study population exposed to vinyl acetate was not clearly identified. There was more than one report from the same study population for lymphohematopoietic cancer (Ott et al. 1989; Union Carbide 1989) and brain cancer (Austin and Schnatter 1983; Leffingwell et al. 1983).

Heck et al. (2024) assessed the association between ambient levels of several air toxics, including vinyl acetate, and breast cancer risk in the Multiethnic Cohort study. Study participants were 48,665 Californian women residing in the greater Los Angeles area who were followed from 2003 through 2013. Residential addresses geocoded for 1998–2000 and 2001–2003 were linked to the 1999 and 2002 National Air Toxics Assessment (NATA) models, respectively, according to 2000 census tracts. The air toxics concentrations were also modeled using the US EPA Assessment System for Population Exposure Nationwide (ASPEN) model in sensitivity analyses; small differences were found between models that did not change the interpretation of the results. The concentrations of air toxics were shown to vary across census tracts (neighborhoods). Vinyl acetate was not highly correlated with any of the other measured air toxics (r^2 ranged from 0.03 with 1,3-butadiene to 0.35 with methyl isobutyl ketone). The mean modeled residential census tract air concentration of vinyl acetate was 8.14 x 10^{-3} µg/m^3 (minimum: 7.93 x 10^{-7} µg/m^3; maximum: 4.87 x 10^{-2} µg/m^3) among all participants and was highest among African Americans compared to Japanese Americans, Latinos, and whites.

Cox proportional hazards models were used to estimate breast cancer risk per one interquartile range (IQR) increase in air toxics exposure lagged by 5-years (Heck et al. 2024). All models were adjusted for race, ethnicity, education, and several other known risk factors for breast cancer. Among all women, increased risks of invasive breast cancer were observed with vinyl acetate exposure (hazard ratio $(HR)_{adjusted}$, 5.27; 95% CI, 4.14–6.73). Increased risks were also observed in analyses stratified by breast cancer subtypes (hormone receptor-positive or -negative) and race/ethnicity, analyses

restricted to non-smokers, and several other sensitivity analyses (using the US EPA ASPEN model, comparing movers and non-movers, adjustment for nitrogen oxides as a marker for traffic pollution, and multiple imputation for missing covariate values). The highest adjusted risk estimates were observed in African Americans (HR, 11.30; 95% CI, 7.36–17.35) and in women with hormone receptor-negative tumors (HR, 7.09; 95% CI, 5.18–9.70). Detailed results are presented in Table 2.

There were several strengths of this study, including large sample size, prospective cohort, multiethnic population, a detailed questionnaire that collected data on multiple covariates, and detailed residential histories available for residents who lived in California during the study period (Heck et al. 2024). This analysis was well powered to study air toxics because it was conducted in an urban setting with high traffic and industrial pollutant levels. A unique feature was the inclusion of neighborhoods comprised primarily of historically marginalized racial and ethnic groups that incurred higher pollution burden.

There were also some limitations in this study regarding exposure assessment. Most importantly, there was some imprecision and uncertainty in the NATA modeled air toxics exposure estimates at the census tract level (US EPA 2015). More localized measurements at individuals' residences or personal monitoring to account for exposures acquired outside of one's residential neighborhood may have enhanced the precision of the exposure assessment. Another limitation is that the list of chemicals assessed was not exhaustive, and it is possible the chemicals studied are correlated with unmeasured chemicals. Finally, exposures occurring earlier in life outside of the study period were not accounted for (Heck et al. 2024).

The rest of the studies were conducted in workers but were considered less informative. In brief, ever having been exposed to vinyl acetate was reported to be associated with an increased risk of brain cancer (though not statistically significant) (Austin and Schnatter 1983; Leffingwell et al. 1983) and lymphohematopoietic cancer (though confidence intervals were not reported) (Ott et al. 1989), but no associations were observed for lung cancer or liver angiosarcoma. Interpretation of each of these studies was limited by small numbers of exposed cases, confidence intervals that were wide or lacked statistical significance or were not reported, and crude methods for assessing exposure to vinyl acetate. For example, most studies assessed only 'ever exposure' to vinyl acetate without further information on intensity, frequency, or duration of exposure. Although the epidemiological studies were conducted in populations potentially highly exposed occupationally to vinyl acetate, co-exposure to multiple chemicals was another challenge to interpreting these data. Co-exposures were generally not accounted for in statistical analysis; hence it is difficult to attribute any cancer outcomes in these workers specifically to exposure to vinyl acetate.

Details of study design and epidemiologic findings for these studies are presented in Table 2.

Table 2. Epidemiological studies of vinyl acetate and cancer (presented by year of publication)

Reference, study-design, location, and year	Population description & exposure assessment method	Cancer site and type	Results			Comments, strengths, and limitations
			Exposure category or level	Risk estimate (95% CI)	Exposed cases or deaths	
Waxweiler et al. (1981) Retrospective cohort and nested case-control designs Kentucky, United States **Enrollment or follow-up:** 1942–1973	**Population**: 4806 white male employees at a synthetic chemicals plant **Exposure assessment method**: expert assessment; employees' detailed work history combined with exposure ratings for 19 chemicals for each job and calendar year since the plant's start in 1942.	Lung cancer	Did not report risk estimates. Reported only cumulative dose difference for vinyl acetate (observed minus expected) in the lung cancer cases. The subgroup with large-cell undifferentiated lung cancer had slightly higher cumulative exposure to vinyl acetate than expected. Observed doses were lower in cases compared to non-cases for all lung cancer and the combined category of adenocarcinoma and large-cell undifferentiated cancers.			**Exposure information:** Observed and expected doses expressed as "dose units" calculated by multiplying an exposure ranking assigned to each employee based on job history and task by number of calendar days worked. Ranking was based on knowing whether a chemical was present in a work area and how it was handled. Co-exposures included: vinyl chloride, acrylonitrile, 1,3-butadiene, acrylamide, vinylidene chloride. **Strengths**: Study design minimizes detection bias (pathologists were blinded) and potential confounding due to age, race, migration. Long follow-up: 63% of the participants achieved 20 years latency, which would be sufficient to detect cancer. **Limitations**: Workers were exposed to multiple chemicals that were not adjusted for in the analysis. Cannot attribute any health effects specifically to vinyl acetate. No quantitative exposure data or measurements of vinyl acetate exposure.

Reference, study-design, location, and year	Population description & exposure assessment method	Cancer site and type	Results			Comments, strengths, and limitations
			Exposure category or level	Risk estimate (95% CI)	Exposed cases or deaths	
Austin and Schnatter (1983) Case-control Texas City, Texas, United States **Enrollment or follow-up:** 1941–1977 Same study population as Leffingwell et al. (1983) but provides additional sensitivity analysis for controls.	**Population:** white male employees at a Union Carbide Corporation chemical plant. **Cases:** 21 (17 gliomas, 4 meningiomas); **Controls:** 2 control groups of 80 employees randomly selected from 450 decedents known to the company in June 1979 (control group 1 excluded employees whose cause of death was attributable to any malignant neoplasm; control group 2 included subjects whose cause of death was attributable to non-brain tumors). "Hourly controls" exclude salaried employees. Control groups identified by NIOSH/UCC researchers. **Exposure assessment method:** company records. UCC industrial hygienists identified principal chemicals used or produced in each department at any time in the history of the plant.	Brain cancer (glioma + meningioma)	OR, ever exposed, Control 1	[1.75 (0.42–7.3)], calculated by OEHHA, see Appendix B	5	**Exposure information:** Employee considered exposed if ever worked in a department associated with that chemical, unexposed if he never worked in such a department, and unknown if he was never known to have been exposed to a chemical but who had ever worked in a department for which no specific chemicals could be listed. Authors state it was not feasible to specify exposure by year because they would have had to rely on memories of former long-term employees. Co-exposures included: vinyl chloride, benzene, ethylene oxide, acetaldehyde, 1,3-butadiene, diethanolamine, methyl isobutyl ketone, styrene, ethylene dichloride, diethyl sulfate, trichloroethane. **Strengths:** Cases confirmed by pathologist at the Armed Forces Institute of Pathology, autopsy report, or histopathology report. **Limitations:** Worker mobility of those employed in maintenance activities is high and thus exposures to specific chemicals cannot be determined with accuracy for approximately half of the
		Brain cancer (glioma + meningioma)	OR, ever exposed, Control 2	[1.64 (0.39–6.98)], calculated by OEHHA, see Appendix B	5	
		Brain cancer (glioma + meningioma)	OR, ever exposed, Hourly Control 1	[1.64 (0.39–6.98)], calculated by OEHHA, see Appendix B	5	
		Brain cancer (glioma + meningioma)	OR, ever exposed, Hourly Control 2	[1.70 (0.39–7.36)], calculated by OEHHA, see Appendix B	5	
		Brain cancer (glioma)	OR, ever exposed, Control 1	[2.19 (0.49–9.76)], calculated by OEHHA, see Appendix B	5	
		Brain cancer (glioma)	OR, ever exposed, Control 2	[2.05 (0.45–9.31)], calculated by OEHHA, see Appendix B	5	

Reference, study-design, location, and year	Population description & exposure assessment method	Cancer site and type	Results			Comments, strengths, and limitations
			Exposure category or level	Risk estimate (95% CI)	Exposed cases or deaths	
	Company records contained job title and department assignment codes for each employee.	Brain cancer (glioma)	OR, ever exposed, Hourly Control 1	[2.05 (0.45–9.31)], calculated by OEHHA, see Appendix B	5	employees. Crude exposure assignment could result in non-differential exposure misclassification.
		Brain cancer (glioma)	OR, ever exposed, Hourly Control 2	[2.13 (0.46–9.83)], calculated by OEHHA, see Appendix B	5	
Leffingwell et al. (1983) Nested case-control Texas City, Texas, United States **Enrollment or follow-up:** 1950–1977 Same study population as Austin and Schnatter (1983)	**Population:** male employees at a Union Carbide Corporation chemicals and plastics plant **Cases:** 17; **Controls:** 6 per case (5 for 1 case), matched by race, year of birth, date of first employment at plant, date of last employment at plant **Exposure assessment method:** company records. Plant personnel indicated which departments used, produced, or redistributed particular chemicals in each department group. Company records were coded with where employees worked and	Brain cancer (glioma)	OR, years of exposure to vinyl acetate (excluding maintenance workers) [a]			**Exposure information:** Ever exposure defined as the presence of a chemical in a department. Industrial hygiene data were available in recent years but unclear how this was used for exposure assignment of individuals. Co-exposures included: vinyl chloride, acetaldehyde, diethanolamine, methyl isobutyl ketone, styrene, diethyl sulfate, ethylene dichloride. **Strengths**: Detailed employee exposure histories were collected. Availability of industrial hygiene data in recent years. Cases confirmed by pathology. **Limitations**: Workers were exposed to multiple chemicals that were not adjusted for in the analysis. No quantitative measurements of vinyl acetate
			0-14 years	3.1 (0.8–12.05)	5	
			15+ years	2.74 (0.57–13.2)	5	
			Ever exposure	3.3 (0.84–12.88)	6	
			OR, years of exposure to vinyl acetate (including maintenance workers) [a]			
			0-14 years	2.67 (0.85–8.38)	11	
			15+ years	1.89 (0.62–5.75)	11	
			Ever exposure	2.47 (0.88–6.94)	13	

Reference, study-design, location, and year	Population description & exposure assessment method	Cancer site and type	Results			Comments, strengths, and limitations
			Exposure category or level	Risk estimate (95% CI)	Exposed cases or deaths	
	verified by NIOSH/OSHA researchers.					exposure. The crude exposure assignment could result in non-differential exposure misclassification.
Ott et al. (1989) Nested case-control **Enrollment or follow-up:** 1940–1978 West Virginia, USA (Kanawha Valley) Same analysis and study population as a pre-publication report (Union Carbide 1989)	**Population**: 29,139 men employed at any one of 3 Union Carbide facilities (2 chemical manufacturing plants, 1 research and development center) over 39-year period and followed for vital status. **Cases**: 52 non-Hodgkin's lymphoma, 20 multiple myeloma, 39 non-lymphocytic leukemia, 18 lymphocytic leukemia; **Controls**: 5 per case, matched on decade of employment & survival to the start of the same 5-year period as cases **Exposure assessment method:** expert assessment; exposure to 21 chemicals with suspected carcinogenicity based on work activity, work area, and production over time. Employee's exposure determined by tracing work assignments and linking assignment records to files on historic	Non-lymphocytic leukemia	OR, ever exposure	0.5 (NR)	2	**Exposure information:** Ever exposure defined as ≥1 day of work with the chemical. 40.5% employees (n=81) were ever exposed to vinyl acetate; 20.5% were exposed for 5+ years. Vinyl acetate was present in 10 work areas and was highly correlated with vinyl chloride and acrylonitrile (Ott et al. 1989). Co-exposures included: vinyl chloride, acetaldehyde, acrylonitrile, benzene, 1,3-butadiene, dioxane, ethylene oxide, formaldehyde, styrene, epichlorohydrin, ethylene dichloride, propylene oxide. **Strengths:** Detailed work histories collected. Use of controls from the same cohort reduces effect of potential confounders **Limitations:** Crude categorization of ever exposure to vinyl acetate, lack of adjustment for co-exposures or potential confounders, few exposed cases. High potential for outcome misclassification from use of death certificates for outcomes other than leukemia and multiple myeloma. If
		Lymphocytic leukemia	OR, ever exposure	1.8 (NR)	2	
		Multiple myeloma	OR, ever exposure	1.6 (NR)	3	
		Non-Hodgkin's lymphoma	OR, ever exposure	1.2 (NR)	7	

Reference, study-design, location, and year	Population description & exposure assessment method	Cancer site and type	Results			Comments, strengths, and limitations
			Exposure category or level	Risk estimate (95% CI)	Exposed cases or deaths	
	departmental usage of each chemical. Potential exposure assumed if employee was assigned to production unit with history of use of that chemical. Job history assessed up to start of 5-year survival interval.					the 'ever exposed' category has a large proportion of workers with low exposure, this would bias risk estimates towards the null.
Lewis and Rampala (2003) Case-cohort Louisville, Kentucky, United States **Enrollment or follow-up:** 1942–2002	**Population:** 6076 employees at a polyvinyl chloride and nitrile rubber copolymer production plant. Comparison cohort limited to 1817 white men hired prior to 1967 who had worked at least 1 year. **Exposure assessment method:** expert assessment; employees' detailed work history combined with ranked chemical exposure estimates for each job, building, and year dating back to 1942.	Angio-sarcoma of the liver	OR, ever exposed to vinyl acetate, adjusted for vinyl chloride exposure	[1.0 (0.994–1.005)], calculated by OEHHA, see Appendix B	NR	**Comment:** OR and 95% CI calculated by OEHHA staff from data reported in logistic regression models [indicated by brackets] **Exposure information:** Semi-quantitative: Job-by-job expert assessment for potential probability, frequency and intensity of exposure. Persons who rotated position/worked in maintenance assigned highest rank for each chemical from all areas the position covered. Cumulative exposure estimates determined by multiplying months worked for each year and job ("cumulative exposure rank months"). Co-exposures included: vinyl chloride, vinylidene chloride, acrylonitrile, 1,3-butadiene, styrene. **Strengths:** Controls selected to eliminate short term employees and ensure ranks were taken from early years when exposures were highest. Logistic

Reference, study-design, location, and year	Population description & exposure assessment method	Cancer site and type	Results			Comments, strengths, and limitations
			Exposure category or level	**Risk estimate (95% CI)**	**Exposed cases or deaths**	
						regression controlled for vinyl chloride exposure. All cases confirmed by hepatologist and pathologist. **Limitations:** Cases were co-exposed to vinyl chloride and other chemicals. No quantitative exposure data or measurements of vinyl acetate exposure.
Heck et al. (2024) Prospective cohort Los Angeles, CA, United States **Enrollment or follow-up:** 1993–2013	**Population:** 48,665 women enrolled in the Multiethnic Cohort **Exposure assessment method:** modeling; National Air Toxics Assessment (NATA) and Hazardous Air Pollutant Exposure Model (HAPEM) used to estimate exposure; linked to geocoded addresses by census tract	Breast	HR, per IQR increase in vinyl acetate, 5-year exposure lagging			**All models adjusted for:** age at entry, race and ethnicity, BMI, family history of breast cancer, age at first live birth, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity, energy intake, alcohol use, smoking, education, neighborhood SES. **Strengths:** Large sample size, prospective cohort, multiethnic population, detailed questionnaire that collected data on multiple covariates, several subgroup and sensitivity analyses were conducted with enough statistical power, and detailed residential histories available for residents who lived in California during the study period. **Limitations:** NATA models only provide air pollution estimates at the census tract level and may reduce
			All women	5.27 (4.14–6.73)	NR	
			Non-smokers	4.82 (3.59–6.48)	NR	
			Hormone receptor-negative (ER- and PR-)	7.09 (5.18–9.70)	NR	
			Hormone receptor-positive (ER+ and PR+)	4.77 (3.70–6.15)	NR	
			African American	11.30 (7.36–17.35)	NR	
			Japanese American	3.81 (2.33–6.24)	NR	

Latinos	4.69 (3.32–6.62)	NR	precision in the estimates. A non-exhaustive list of chemicals was assessed which may be correlated with other unmeasured chemical exposures. Important earlier life exposures may be missed due to estimating exposures only during the study period.
Whites	5.71 (4.04–8.06)	NR	
Non-movers only	6.76 (4.63–9.87)	NR	
Movers only	5.28 (4.14–6.73)	NR	
Additional adjust-ment for NO_x (nitrogen oxides)	5.45 (4.28–6.94)	NR	
Multiple imputa-tion for missing covariate values	4.28 (3.49–5.25)	NR	
Exposure estimated using US EPA ASPEN model	4.71 (3.77–5.88)	NR	

NR, not reported; OR, odds ratio; HR, hazard ratio; IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor; NOx, nitrogen oxides; SES, Socioeconomic status

[a] 90% CIs, calculated by study authors.

4. CARCINOGENICITY STUDIES IN ANIMALS

OEHHA identified multiple carcinogenicity studies of vinyl acetate in animals, with 16 studies in rats and 8 studies in mice. Tables 3 through 6 provide an overview of the available carcinogenicity studies in rats and mice, organized by age/life stage at first exposure[5] :

- Table 3: rats; exposures starting at 6 weeks of age or later
- Table 4: rats; early life exposures (preconception and/or *in utero*, and continuing after birth)
- Table 5: mice; exposures starting at 6 weeks of age or later
- Table 6: mice; early life exposures (*in utero*, and continuing after birth)

In rats, there were 10 studies in which exposure started at 6 weeks of age or later, with two inhalation studies in Sprague-Dawley (SD) derived Crl:CD(SD)BR rats, and 8 drinking water studies in Fischer 344, F344/DuCrj, SD and Wistar rats (Table 3). In addition, there were 6 drinking water studies with vinyl acetate exposure starting pre-conception or *in utero* and continuing after birth in Crl:CD(SD)BR, SD and Wistar rats (Table 4). In mice, 6 studies in which exposure started at 6 weeks of age or later were identified, with two inhalation studies conducted in Swiss derived Crl:CD-1(ICR)BR mice, and four drinking water studies in Crj:BDF1 and Swiss mice (Table 5). Additionally, two drinking water studies with exposure beginning *in utero* and continuing after birth were reported in Swiss mice (Table 6).

As indicated in these overview tables of the vinyl acetate animal carcinogenicity studies, some studies had small numbers of animals (n ≤ 20) per dosing group (Belpoggi et al. 2002; EPL 1982; Lijinsky and Reuber 1983; Maltoni et al. 1997; Minardi et al. 2002).

Given that acetaldehyde, a metabolite of vinyl acetate, has been classified as a “Group 2B” carcinogen (possibly carcinogenic to humans) by IARC since 1987 (IARC 1987, 1999) and as “Reasonably anticipated to be a human carcinogen” by the NTP RoC since 1991 (NTP 2021), the tumor findings from animal carcinogenicity studies of acetaldehyde are briefly summarized in section 4.3.2. Both IARC and the NTP RoC concluded there is sufficient evidence of carcinogenicity for acetaldehyde in experimental animals.

[5] For ease of identifying studies for each species, the studies in rats are continually numbered in Tables 3 and 4, and the studies in mice are continually numbered in Tables 5 and 6.

Table 3. Carcinogenicity studies of vinyl acetate in rats with exposures starting at 6 weeks of age or later

No.	Strain	Sex, group size	Route, age at first exposure	Administered concentration (in air or drinking water)	Exposure duration (weeks)	Reference
1	Crl:CD(SD)BR	M, 60	Inhalation, 6 weeks (45 days)	0, 50, 200, 600 ppm	104	Bogdanffy et al. (1994a), Owen (1988)
2	Crl:CD(SD)BR	F, 60	Inhalation, 6 weeks (45 days)	0, 50, 200, 600 ppm	104	Bogdanffy et al. (1994a), Owen (1988)
3	Fischer 344	M, 20	Drinking water, 7 to 8 weeks	0, 1000, 2500 ppm[1]	100	Lijinsky and Reuber (1983), EPL (1982)
4	Fischer 344	F, 20	Drinking water, 7 to 8 weeks	0, 1000, 2500 ppm[1]	100	Lijinsky and Reuber (1983), EPL (1982)
5	F344/DuCrj	M, 50	Drinking water, 6 weeks	0, 400, 2000, 10000 ppm	104	Umeda et al. (2004), JBRC (1995)
6	F344/DuCrj	F, 50	Drinking water, 6 weeks	0, 400, 2000, 10000 ppm	104	Umeda et al. (2004), JBRC (1995)
7	SD	M, 13–14	Drinking water, 17 weeks	0, 1000, 5000 ppm	104	Minardi et al. (2002)
8	SD	F, 37	Drinking water, 17 weeks	0, 1000, 5000 ppm	104	Minardi et al. (2002)
9	Wistar	M, 13–14	Drinking water, 17 weeks	0, 1000, 5000 ppm	104	Belpoggi et al. (2002)
10	Wistar	F, 37	Drinking water, 17 weeks	0, 1000, 5000 ppm	104	Belpoggi et al. (2002)

SD, Sprague-Dawley; ppm, parts per million; M, male; F, female.
[1] Authors reported the administered doses in mg/L (OEHHA assumes 1 mg vinyl acetate/L is equivalent to 1 ppm).

Table 4. Carcinogenicity studies of vinyl acetate in rats (F_1) with pre-conception and/or *in utero* exposures that continued after birth

No.	Strain	Sex, group size	Exposure route, design, and duration	Administered concentration in drinking water	Reference
11	Crl:CD(SD)BR	M, 60	(F_0: via drinking water) F_1: pre-conception, *in utero*, and through lactation (via F_0), via drinking water from weaning until 104 weeks of age	0, 200, 1000, 5000 ppm	Bogdanffy et al. (1994b); Shaw (1988)
12	Crl:CD(SD)BR	F, 60	(F_0: via drinking water) F_1: pre-conception, *in utero*, and through lactation (via F_0), via drinking water from weaning until 104 weeks of age	0, 200, 1000, 5000 ppm	Bogdanffy et al. (1994b); Shaw (1988)
13	SD	M, 53–107	(F_0: via drinking water) F_1: *In utero* from GD12 and through lactation (via F_0), via drinking water from weaning until 104 weeks of age	0, 1000, 5000 ppm	Minardi et al. (2002)
14	SD	F, 57–99	(F_0: via drinking water) F_1: *In utero* from GD12 and through lactation (via F_0), via drinking water from weaning until 104 weeks of age	0, 1000, 5000 ppm	Minardi et al. (2002)
15	Wistar	M, 64–86	(F_0: via drinking water) F_1: *In utero* from GD12 and through lactation (via F_0), via drinking water from weaning until 104 weeks of age	0, 1000, 5000 ppm	Belpoggi et al. (2002)
16	Wistar	F, 69–95	(F_0: via drinking water) F_1: *In utero* from GD12 and through lactation (via F_0), via drinking water from weaning until 104 weeks of age	0, 1000, 5000 ppm	Belpoggi et al. (2002)

F_0, breeder animals; F_1, offspring; SD, Sprague-Dawley; ppm, parts per million; M, male; F, female; GD, gestation day.

Table 5. Carcinogenicity studies of vinyl acetate in mice with exposures starting at 6 weeks of age or later

No.	Strain	Sex, group size	Route, age at first exposure	Administered concentration (in air or drinking water)	Exposure duration (weeks)	Reference
1	Swiss (Crl:CD-1(ICR)BR)	M, 60	Inhalation, 6 weeks (45 days)	0, 50, 200, 600 ppm	104	Bogdanffy et al. (1994a), Owen (1988)
2	Swiss (Crl:CD-1(ICR)BR)	F, 60	Inhalation, 6 weeks (45 days)	0, 50, 200, 600 ppm	104	Bogdanffy et al. (1994a), Owen (1988)
3	Crj:BDF1	M, 50	Drinking water, 6 weeks	0, 400, 2000, 10000 ppm	104	Umeda et al. (2004), JBRC (1995)
4	Crj:BDF1	F, 50	Drinking water, 6 weeks	0, 400, 2000, 10000 ppm	104	Umeda et al. (2004), JBRC (1995)
5	Swiss	M, 13–14	Drinking water, 17 weeks	0, 1000, 5000 ppm	78	Maltoni et al. (1997)
6	Swiss	F, 37	Drinking water, 17 weeks	0, 1000, 5000 ppm	78	Maltoni et al. (1997)

ppm, parts per million; M, male; F, female

Table 6. Carcinogenicity studies of vinyl acetate in mice (F_1) with *in utero* exposures that continued after birth

No.	Strain	Sex, group size	Exposure route and design	Administered concentration in drinking water	Reference
7	Swiss	M, 37–49	(F0: via drinking water) F1: *In utero* from GD12 and through lactation (via F_0), and via drinking water from weaning until 78 weeks of age	0, 1000, 5000 ppm	Maltoni et al. (1997)
8	Swiss	F, 44–48	(F0: via drinking water) F1: *In utero* from GD12 and through lactation (via F_0), and via drinking water from weaning until 78 weeks of age	0, 1000, 5000 ppm	Maltoni et al. (1997)

F_0, breeder animals; F_1, offspring; ppm, parts per million; M, male; F, female; GD, gestation day

4.1 Carcinogenicity Studies in Rats

4.1.1 104-week inhalation studies in male and female Crl:CD(SD)BR rats (Bogdanffy et al. 1994a; Owen 1988)

104-week inhalation studies in male and female Crl:CD(SD)BR rats were reported by Hazleton Laboratories UK (Owen 1988) and the data were published in a peer-reviewed article (Bogdanffy et al. 1994a).

Male and female Crl:CD(SD)BR rats, an outbred strain derived from Sprague-Dawley rats, were administered 0, 50, 200, or 600 ppm vinyl acetate by inhalation (6 hours per day, 5 days per week, except two holidays per year), starting at 45 days of age, for 104 weeks. In each study, each experimental group comprised of 60 animals. Average daily doses were calculated to be 0, 26, 104, and 312 mg/kg-day for males, and 0, 31, 124, and 371 mg/kg-day for females. The purity of vinyl acetate used in the studies was > 99%, with some impurities reported, including acetic acid (≤ 10 ppm) and acetaldehyde (≤ 65 ppm).

It is worth noting that in these studies not all tissues from all animals on study underwent histological examination. The Owen (1988) report indicates that all tissues were examined during gross necropsy, but only the following were examined histologically[6]:

- Respiratory tract tissues from all animals
- All tissues from control and high-dose animals
- Tissues (from any group) found to be abnormal during gross necropsy

Therefore, it is reasonable to conclude that the tissues (other than the respiratory tract) from low- and mid-dose animals were not adequately examined via histology.

Males

In males, the mortality in the dosed groups was not significantly different from the control group. The average body weight in the 600 ppm (high-dose) group was statistically significantly lower than that of the controls.

Table 7 presents the vinyl acetate treatment-related respiratory tract tumors observed in this study. Five rare squamous cell papillomas were observed in the nasal cavity, with four inverted, endophytic papillomas occurring at the 600 ppm (high-dose) group and one exophytic papilloma in the 200 ppm (mid-dose) group. The increase of papillomas

[6] Regarding this issue, Bogdanffy et al. (1994a) states that “tissues from animals in the control and 600 ppm concentration groups (and respiratory tract tissues from animals in the 50 and 200 ppm concentration groups) and from all animals that died or were killed *in extremis* were embedded in paraffin wax, sectioned at 5 µm, stained with hematoxylin and eosin, and examined microscopically”.

showed a statistically significant trend. Additionally, two rare squamous cell carcinomas and one rare carcinoma *in situ* were observed at the high-dose group. The total incidence of nasal tumors was significantly higher in the high-dose group compared to the control group, with a significant dose-related trend.

Spontaneous occurrence of nasal neoplasms is rare in male rats (Herbert et al. 2018). Laboratory historical control data for nasal neoplasms in male Crl:CD(SD)BR rats were not reported by Owen (1988) or Bogdanffy et al. (1994a). The spontaneous rate of nasal cavity tumors observed in a different, but related substrain [Crl:CD(SD)] of male rats from two-year studies initiated between 1991 and 2002 in a different laboratory [Charles River Laboratories] was 0.05% (1/2146, 30 studies, ranging from 0 to 2%) (CRL 2004).

Table 7. Incidence of respiratory tract tumors in male Crl:CD(SD)BR rats administered vinyl acetate by inhalation for 104 weeks (Bogdanffy et al. 1994a; Owen 1988)

Tumor site	Tumor type (week of first tumor)	Administered concentration in air (ppm)				Trend test *p*-value
		0	50	200	600	
Nasal cavity	Squamous cell papilloma (r) (103 weeks)	0/36	0/28	1/35	4/40	< 0.01
	Squamous cell carcinoma (r) (103 weeks)	0/36	0/28	0/35	2/40	NS
	Carcinoma *in situ* (r) (103 weeks)	0/36	0/28	0/35	1/40	NS
	Total tumors (r) (103 weeks)	0/36	0/28	1/35	7/40**	< 0.001

Tumor incidence is expressed as the number of tumor-bearing animals (Bogdanffy et al. 1994a) over the number of animals alive at the time of first occurrence of the tumor (Owen 1988).

Bogdanffy et al. (1994a) states the following: “Two histopathological evaluations were conducted. The first was conducted at Hazleton Laboratories, UK. Following the initial review by Hazleton Laboratories UK, a second, independent, and more detailed review of the respiratory tract tissues was conducted at the TNO-CIVO laboratories in the Netherlands. The descriptions of histopathology primarily follow those from the TNO Laboratory rather than those from Hazleton UK.” There are some differences in the classifications of these nasal tumors but not in the total number of animals bearing nasal tumors, and the description of tumors in this table is based on pathological evaluation from Bogdanffy et al. (1994a).

Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): ** $p < 0.01$. Exact trend test conducted by OEHHA. NS, not significant; (r), rare tumor, see text for details.

Non-neoplastic pathology findings

A variety of non-neoplastic lesions in the olfactory epithelium of the nasal cavity were reported, including basal cell hyperplasia, squamous metaplasia, atrophy, regeneration, and inflammatory cell infiltrate (Table 8).

Table 8. Non-neoplastic lesions in the nasal cavity in male rats (Bogdanffy et al. 1994a)

Non-neoplastic finding and severity	Administered concentration in air (ppm)			
	0	50	200	600
Olfactory epithelial basal cell hyperplasia				
Slight	0/59	0/60	40/59***	21/59***
Moderate	0/59	0/60	11/59***	22/59***
Olfactory epithelial squamous metaplasia				
Slight	0/59	0/60	0/59	12/59**
Moderate	0/59	0/60	0/59	9/59**
Olfactory epithelial atrophy				
Slight	0/59	2/60	47/59***	7/59*
Moderate	0/59	0/60	2/59	33/59***
Severe	0/59	0/60	0/59	10/59***
Olfactory epithelial regeneration				
Slight	0/59	0/60	30/59***	1/59
Olfactory epithelial inflammatory cell infiltrate				
Slight	0/59	0/60	0/59	7/59**

Incidences were reported by Bogdanffy et al. (1994a) and the denominators represent the number of animals from which this tissue was examined microscopically. Treatment group incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

Females

Starting at approximately week 86, survival of female rats was greater in the high-dose group compared to controls, and by week 102 survival in the high-dose group was 28% greater than in the controls. A statistically significant decrease in average body weight was observed in the high-dose group compared to controls at the end of the 104-week study.

Vinyl acetate treatment-related respiratory tract tumors in female Crl:CD(SD)BR rats observed in the 104-week study are presented in Table 9. A non-significant increase in rare nasal squamous cell carcinomas was observed in the high-dose group. Additionally, a rare laryngeal squamous cell carcinoma was found in the high-dose group.

Spontaneous occurrences of nasal cavity and larynx tumors are rare in female rats (Herbert et al. 2018). Laboratory historical control data for nasal and larynx neoplasms in female Crl:CD(SD)BR rats were not reported by Owen (1988) or Bogdanffy et al. (1994a). No spontaneous nasal or laryngeal tumors were observed in a different, but related substrain [Crl:CD(SD)] of female rats in 31 two-year studies initiated between 1991 and 2002 in a different laboratory [Charles River Laboratories] (0/2344) (CRL 2004).

Table 9. Incidence of respiratory tract tumors in female Crl:CD(SD)BR rats administered vinyl acetate by inhalation for 104 weeks (Bogdanffy et al. 1994a; Owen 1988)

Tumor site	Tumor type (week of first tumor)	Administered concentration in air (ppm)				Trend test *p*-value
		0	50	200	600	
Nasal cavity	**Squamous cell carcinoma (r) (95 weeks)**	0/34	0/37	0/41	4/46	< 0.01
Larynx	**Squamous cell carcinoma (r) (95 weeks)**	0/33	0/37	0/39	1/44	NS

Tumor incidence is expressed as the number of tumor-bearing animals (Bogdanffy et al. 1994a) over the number of animals alive at the time of first occurrence of the tumor (Owen 1988).

Bogdanffy et al. (1994a) states the following: “Two histopathological evaluations were conducted. The first was conducted at Hazleton Laboratories, UK. Following the initial review by Hazleton Laboratories UK, a second, independent, and more detailed review of the respiratory tract tissues was conducted at the TNO-CIVO laboratories in the Netherlands. The descriptions of histopathology primarily follow those from the TNO Laboratory rather than those from Hazleton UK.” There are some differences in the classifications of these nasal tumors but not in the total number of animals bearing nasal tumors, and the description of tumors in this table is based on pathological evaluation from Bogdanffy et al. (1994a).

Exact trend test conducted by OEHHA.
NS, not significant; (r), rare tumor, see text for details.

Non-neoplastic pathology findings

A variety of non-neoplastic lesions in the nasal cavity were reported in the female rats, including basal cell hyperplasia, squamous metaplasia, atrophy, regeneration, and

inflammatory cell infiltrate of the olfactory epithelium, and submucosal inflammatory cell infiltrate (Table 10).

Table 10. Non-neoplastic lesions in nasal cavity of female rats (Bogdanffy et al. 1994a)

Non-neoplastic finding and severity	Administered concentration in air (ppm)			
	0	50	200	600
Olfactory epithelial basal cell hyperplasia				
Very slight	0/60	0/60	7/60**	0/59
Slight	0/60	0/60	24/60***	35/59***
Moderate	0/60	0/60	3/60	16/59***
Olfactory epithelial squamous metaplasia				
Slight	0/60	0/60	0/60	26/59***
Moderate	0/60	0/60	0/60	7/59**
Olfactory epithelial atrophy				
Slight	0/60	0/60	23/60***	18/59***
Moderate	0/60	0/60	0/60	30/59***
Olfactory epithelial regeneration				
Slight	0/60	0/60	16/60***	7/59**
Olfactory epithelial inflammatory cell infiltrate				
Slight	0/60	0/60	0/60	5/59*
Submucosal inflammatory cell infiltrate				
Moderate	0/60	0/60	0/60	5/59*

Incidences were reported by Bogdanffy et al. (1994a) and the denominators represent the number of animals from which this tissue was examined microscopically. Treatment group incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

4.1.2 100-week drinking water studies in male and female Fischer 344 rats (EPL 1982; Lijinsky and Reuber 1983)

100-week drinking water studies in male and female Fischer 344 rats were conducted by the National Cancer Institute (NCI) and the data were published in a peer-reviewed article (Lijinsky and Reuber 1983). Regarding histological examination, Dr. Lijinsky mentioned in a cover letter transmitting a pathology report to the US EPA (see EPL

1982) that not all tissues of all animals were examined and reported in the publication (Lijinsky and Reuber 1983). With Dr. Lijinsky's consent and NCI's concurrence, the histology slides from these studies were independently examined and reviewed by Environmental Pathology Laboratories, Inc., as well as additional slides prepared from previously unexamined tissues from these studies (EPL 1982).

Male and female Fischer 344 rats at 7–8 weeks of age (20 animals per group) were administered 0, 1000, or 2500 mg/L (ppm) vinyl acetate in drinking water 5 days per week for 100 weeks and observed up to additional 30 weeks. Based on the lifetime administered doses reported by Lijinsky and Reuber (1983) in g/kg bodyweight, average daily doses were calculated to be 0, 50, and 124 mg/kg-day for males, and 0, 80, and 200 mg/kg-day for females. The authors reported the vinyl acetate used in the studies was a "commercial product with no significant impurities" and the rate of vinyl acetate decomposition in the drinking water solutions was 8.5% per day at room temperature and 5% per day at 4°C. In the studies, vinyl acetate solutions were prepared once a week and dispensed into feeding bottles once every three days. Considering the degradation of vinyl acetate in these solutions, the authors noted that the animals likely received lower but at least half of the intended dose.

Males

The survival in the dosed groups was not significantly different from the control group in males. No treatment-related tumor findings were observed in males in the long-term drinking water study.

Females

The survival in the dosed groups was not significantly different from the control group in females. Table 11 presents the treatment-related tumors in the liver, uterus, thyroid, and pituitary gland of female rats. A statistically significant increase in liver neoplastic nodules (hepatocellular adenomas)[7] was observed in the high-dose group. Rare uterine adenocarcinomas were observed in the low- and high- dose groups, with a statistically significant trend. A statistically significant increase in endometrial stromal polyps of the uterus was observed at the high dose compared to the control group, with a statistically significant trend. In addition, one uterine adenoma was observed at the high dose, and one endometrial stromal sarcoma was observed at the low dose. A statistically significantly increase in C-cell adenomas of the thyroid gland was observed at the high dose, with a statistically significant trend. Incidences of pituitary adenomas were increased with a statistically significant dose-related trend.

[7] Neoplastic nodule is an older term used for hepatocellular adenoma, although now the term hepatocellular adenoma is preferred (Bannasch and Zerban, 1990).

Spontaneous occurrence of uterine adenoma or adenocarcinoma, and endometrial stromal sarcoma are rare in female Fischer 344 rats. Spontaneous uterine carcinoma occurred at a rate of 0.4% (4/1001, 20 studies, ranging from 0 to 2%) in female Fischer 344 rats in two-year studies conducted between 1984 to 1994 (NTP 1999). The spontaneous rate was 0.3% (3/1001, 20 studies, ranging from 0 to 4%) for uterine adenomas, and 0.5% (5/1001, 20 studies, ranging from 0 to 4%) for endometrial stromal sarcomas (NTP 1999).

Table 11. Tumor incidence in female Fischer 344 rats administered vinyl acetate in drinking water for 100 weeks (EPL 1982; Lijinsky and Reuber 1983)

Tumor site	Tumor Type	Administered concentration in drinking water (ppm)			Trend test *p*-value
		0	1000	2500	
Liver	**Neoplastic nodule (hepatocellular adenoma)**	0/20	0/20	6/20**	< 0.001
Uterus	**Adenocarcinoma (r)**	0/18	1/20	4/20	< 0.05
	Endometrial stromal polyp	0/18	3/20	5/20*	< 0.05
Thyroid gland	**C-cell adenoma**	0/17	2/19	5/20*	< 0.05
	C-cell carcinoma	1/17	0/19	1/20	NS
	C-cell adenoma and carcinoma (combined)	1/17	2/19	6/20	< 0.05
Pituitary[1]	**Adenoma**	6/17	8/19	12/18	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals from which the particular tissue was examined, as reported by EPL (1982).
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$; ** $p < 0.01$.
Exact trend test conducted by OEHHA.
(r), rare tumor, see text for details; NS, not significant.
[1] Incidence of pituitary carcinoma was reported as 2/17 (control), 1/19 (1000 ppm), 0/18 (2500 ppm) (EPL 1982; Lijinsky and Reuber 1983). There was not enough information to derive combined incidences of benign and malignant tumors of the pituitary gland.

Non-neoplastic pathology findings

In the liver, statistically significant increases in multifocal necrosis (control, 0/20; low-dose, 7/20, $p < 0.05$; high-dose, 4/20) and multifocal vacuolation (control, 1/20; low-dose, 7/20, $p < 0.05$, high-dose, 5/20) were observed at the low dose compared to the controls. In the thyroid, a statistically significant increase in C-cell hyperplasia was observed at the low dose compared to the controls (control, 2/17; low-dose, 8/19, $p < 0.05$; high-dose, 3/20) (EPL 1982).

4.1.3 104-week drinking water studies in male and female F344/DuCrj rats (JBRC 1995; Umeda et al. 2004)

104-week drinking water studies in male and female F344/DuCrj rats were reported by the Japan Bioassay Research Center (JBRC 1995) and the data were later published in a peer-reviewed article (Umeda et al. 2004).

Male and female F344/DuCrj rats at 6 weeks of age (50 animals per group) were administered 0, 400, 2,000 or 10,000 ppm vinyl acetate (> 98% purity) in drinking water for 104 weeks. Average daily intakes were 0, 21, 98, and 442 mg/kg-day for males, and 0, 31, 146, and 575 mg/kg-day for females in the two-year studies (Umeda et al. 2004). vinyl acetate solutions were prepared twice a week during the studies. The authors reported that the concentrations of vinyl acetate in the administered solutions decreased to 72-80% of the starting concentrations due to evaporation four days after preparation, likely resulting in lower doses than intended. Additionally, they noted that concentrations of acetic acid in the prepared solutions increased with higher concentrations of vinyl acetate. Acetic acid concentrations were 9.2 ppm for the 400-ppm solution, 47 ppm for the 2000 ppm solution, and 263 ppm for the 10,000-ppm solution.

Males

In males, the survival rates in the dosed groups were not significantly different from those of the control group. The average body weight in the 10000 ppm (high-dose) group was statistically significantly lower than that of the controls ($p < 0.01$) at the end of the study. Necropsy was performed on all animals. All major organs were examined for histopathology.

Tumors were observed in the oral cavity and testes of male rats in the 104-week drinking water study (Table 12). This study defined oral cavity tumors as tumors of the hard palate, buccal mucosa, gingiva, and lip mucosa. There were statistically significant increases in rare squamous cell carcinoma, and squamous cell papilloma and carcinoma combined of the oral cavity at the high dose.

Spontaneous squamous cell tumors of the oral cavity are rare in male F344/DuCrj rats. In historical studies conducted in male rats at JBRC from 1987 to 2002, no occurrence of squamous cell carcinoma (0/1199) was observed and squamous cell papillomas were observed at a rate of 0.25% or 3/1199 (Umeda et al. 2004).

A statistically significant trend was observed in the incidences of testicular interstitial cell tumors.

Table 12. Tumor incidence in male F344/DuCrj rats administered vinyl acetate in drinking water for 104 weeks (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration in drinking water (ppm)				Trend test *p*-value [1]
		0	400	2000	10000	
Oral Cavity (including lip mucosa)	Squamous cell papilloma (r)	0/50	0/50	0/50	2/50	NS
	Squamous cell carcinoma (r)	0/50	0/50	0/50	5/50*	< 0.001
	Squamous cell papilloma and carcinoma combined (r)	0/50	0/50	0/50	7/50**	< 0.0001
Testes	Interstitial cell tumor	42/50	40/50	44/50	47/50	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals from which the tissue was examined. The combined incidence of oral cavity papilloma and carcinoma was reported by JBRC (1995).
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$.
NS, not significant; (r), rare tumor, see text for details.
[1] Results of exact trend test conducted by OEHHA. JBRC (1995) performed the Cochran-Armitage trend test and three types of Peto trend tests, namely standard method, prevalence method, and combined analysis. Standard method was referred to as “death analysis”, prevalence method was referred to as “incidental tumor test”, and the combined analysis was referred to as “death analysis + incidental tumor test”. For oral cavity squamous cell carcinoma, the following trend test p-values were reported by JBRC (1995): $p < 0.001$ Cochran-Armitage test, $p < 0.05$ standard method, $p < 0.01$ prevalence method, $p < 0.001$ combined analysis. All three p-values for the Peto test were presented by JBRC with a note that “the conditional probabilities of the largest and smallest possible outcomes cannot be estimated or this p-value is beyond the estimated p-value”. For oral cavity squamous cell papilloma and carcinoma combined, the following trend test p-values were reported by JBRC (1995): $p < 0.001$ Cochran-Armitage test, $p < 0.05$ standard method, $p < 0.001$ prevalence method, $p < 0.001$ combined analysis. All four p-values were presented by JBRC with a note that “the conditional probabilities of the largest and smallest possible outcomes cannot be estimated or this p-value is beyond the estimated p-value”. For testicular interstitial cell tumor, the following trend test p-values were reported by JBRC (1995): $p > 0.05$ Cochran-Armitage test, $p < 0.05$ prevalence method (p-values for Peto test standard method and combined analysis were not applicable).

Non-neoplastic pathology findings

JBRC (1995) reported 2/50 male rats in the high-dose group had basal cell activation[8] in the oral cavity, compared to none in the other groups. JBRC (1995) considered the basal cell activation to be a growth-related cell change and a lesion that represents an early stage of cancer.

Females

In females, the survival rates in the dosed groups were not significantly different from those of the controls. There were no significant differences in average body weights between treated groups and the controls. Necropsy was performed on all animals. All major organs were examined for histopathology.

Tumors were observed in the oral cavity and thyroid and mammary glands of female rats in the 104-week drinking water study (Table 13). There was a statistically significant trend in the incidences of rare oral cavity squamous cell carcinomas. Statistically significant increases in thyroid C-cell adenomas, and adenoma and carcinoma combined were observed in the mid-dose group (2000 ppm), compared to controls.

Spontaneous occurrence of oral cavity squamous cell carcinoma is rare in female F344/DuCrj rats, with a rate of 0.09% (1/1147) in historical studies conducted at JBRC from 1987 to 2002 (Umeda et al. 2004).

[8] The same finding was referred to as “basal cell activation” by the JBRC (1995) report, and “basal cell hyperplasia” in the publication by Umeda et al. (2004).

Table 13. Tumor incidence in female F344/DuCrj rats administered vinyl acetate in drinking water for 104 weeks (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration in drinking water (ppm)				Trend test *p*-value [1]
		0	400	2000	10000	
Oral cavity (including lip mucosa)	**Squamous cell carcinoma (r)**	0/50	1/50	1/50	3/50	< 0.05
Thyroid	**C-cell adenoma**	2/50	7/50	8/50*	5/50	NS
	C-cell carcinoma	0/50	0/50	1/50	2/50	NS
	Combined	2/50	7/50	9/50*	6/50	NS
Mammary gland [2]	**Adenocarcinoma**	0/50	0/50	0/50	3/50	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals from which the tissues of interest were examined. The combined incidence for C-cell adenoma and carcinoma was reported by JBRC (1995).
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$.
NS, not significant; (r) denotes a rare tumor, see text for details.
[1] Results of exact trend test conducted by OEHHA. JBRC (1995) performed the Cochran-Armitage trend test and three types of Peto trend tests, namely standard method, prevalence method, and combined analysis. Standard method was referred to as “death analysis”, prevalence method was referred to as “incidental tumor test”, and the combined analysis was referred to as “death analysis + incidental tumor test”. For oral cavity squamous cell carcinoma, the following trend test p-values were reported by JBRC (1995): $p > 0.05$ Cochran-Armitage test, $p < 0.05$ prevalence method (Peto test standard method and combined analysis were not applicable). For thyroid gland C-cell adenoma and carcinoma combined, the following trend test p-values were reported by JBRC (1995): $p > 0.05$ Cochran-Armitage test, $p > 0.05$ prevalence method (Peto test standard method and combined analysis were not applicable). For mammary gland adenocarcinoma, the following trend test p-values were reported by JBRC (1995): $p < 0.01$ Cochran-Armitage test, $p > 0.05$ standard method, $p < 0.05$ prevalence method, $p < 0.01$ combined analysis. The p-values for prevalence and combined analysis were presented by JBRC with a note that “the conditional probabilities of the largest and smallest possible outcomes cannot be estimated or this p-value is beyond the estimated p-value”.
[2] Tumor incidence of mammary gland was reported by JBRC (1995) but not Umeda et al. (2004).

Non-neoplastic pathology findings

A statistically significant increase in basal cell activation was observed in the high-dose group in the stomach (control, 0/50; low-dose, 0/50; mid-dose, 0/50, high-dose, 5/50, $p < 0.05$). One female rat in the high-dose group had basal cell activation in the oral cavity, compared to none in the other groups. JBRC (1995) considered the basal cell activation to be a growth-related cell change and a lesion that represents an early stage of cancer.

4.1.4 104-week drinking water studies in male and female F_1 Crl:CD(SD)BR rats exposed via parental exposure preconception, maternal exposure in utero and during lactation, and direct consumption of drinking water from weaning to 104 weeks of age (Bogdanffy et al. 1994b; Shaw 1988)

104-week drinking water studies in male and female F_1 Crl:CD(SD)BR rats (Sprague-Dawley derived outbred strain) exposed throughout all life stages (preconception, *in utero*, and continuing after birth until 104 weeks of age) were reported by Hazleton Laboratories UK (Shaw 1988) and the data were published in a peer-reviewed article (Bogdanffy et al. 1994b).

Male (n = 72) and female (n = 144) Crl:CD(SD)BR breeder (F_0) rats were administered 0, 200, 1000, 5000 ppm (v/v) vinyl acetate in drinking water for 10 weeks before mating, and throughout mating, gestation and lactation. At weaning, male and female F_1 pups (60 animals per group) were exposed to 0, 200, 1000, or 5000 ppm of vinyl acetate in drinking water for 104 weeks, at which time the study was terminated. Lifetime average daily doses were 0, 10, 47, and 202 mg/kg-day for F_1 males, and 0, 16, 76, and 302 mg/kg-day for F_1 females (Bogdanffy et al. 1994b). Fresh vinyl acetate solutions were prepared daily. The authors reported that impurities in the vinyl acetate test material included acetic acid (≤ 11.5 ppm), acetaldehyde (≤ 71 ppm) and hydroquinone (≤ 1 ppm) (Bogdanffy et al. 1994b).

Males

In F_1 males, the mortality in dosed groups was not significantly different from that of the control group. At weaning, the mean bodyweight in the 5000 ppm (high-dose) group was statistically significantly lower than that of the control. Throughout the study, the mean body weight gain in the 5000-ppm group remained statistically significantly lower than that of the controls. Sporadic decreases in body weights in the 200 ppm (low-dose) group were observed. The authors noted no significant effects on body weight gain in the 200 ppm or 1000 ppm groups (low- or mid-dose).

Two squamous carcinomas of the oral cavity were observed in the high-dose F_1 group (n = 60).

Squamous carcinoma of the oral cavity is a rare tumor type in Crl:CD(SD) rats. The spontaneous rate is 0.09% (2/2146, ranging from 0–2.67%) in males among 30 studies initiated between 1991 and 2000 (CRL 2004). However, Bogdanffy et al. (1994b) noted that “all neoplasms that were observed were typical and within normal biological variation for this age and strain of rat”.

Females

In F_1 females, the mortality in dosed groups was not significantly different from that of the control group. At weaning, the mean bodyweight in the 5000 ppm (high-dose) group

was statistically significantly lower than that of the control, possibly due to *in utero* and lactational exposures to vinyl acetate. The mean body weight gain in the high-dose group was statistically significantly lower than that of the control group during the second year of the study. The authors noted no significant effects on body weight gain in the 200-ppm or 1000-ppm groups (low- or mid-dose).

There were no treatment-related tumor findings in this study of F_1 females.

4.1.5 104-week drinking water studies in male and female parental (F_0) and offspring (F_1) Sprague-Dawley rats (Minardi et al. 2002)

This section discusses results from a set of four studies in Sprague-Dawley rats (male F_0, male F_1, female F_0, and female F_1).

Male (n = 13–14) and female (n = 37) breeder or parental (F_0) Sprague-Dawley rats were administered 0, 1000, or 5000 ppm of vinyl acetate in drinking water starting from 17 weeks of age and continuing for 104 weeks. Male (n = 53–107) and female (n = 57–99) F_1 rats were exposed to 0, 1000, or 5000 ppm of vinyl acetate *in utero* starting on gestation day 12, through lactation, and post-weaning in drinking water until 104 weeks of age. At the end of the treatment period all animals then received tap water until natural death. The average daily dose information (mg/kg-day) was not reported, and such information is unavailable because water consumption data were not provided. The purity of vinyl acetate was >99%, with the following impurities reported: benzene (30–45 ppm), methyl and ethyl acetate (50 ppm), crotonaldehyde (6–16 ppm), acetaldehyde (2–11 ppm), and acetone (330–500 ppm).

Male F_0 and F_1 studies

The authors reported that there were no substantial differences between treated and control F_0 males in mean body weight, survival, or behavior. Similarly, no substantial differences in these parameters were observed between treated and control F_1 males.

Table 14 presents tumor findings observed in males in the two studies.

In F_0 males, a statistically significant increase in pancreatic islet cell adenomas was observed at the high dose, with a statistically significant trend.

In F_1 males, tumors were observed at multiple sites. Squamous cell carcinomas of the “oral cavity and lips” were statistically significantly increased at the high dose, with a statistically significant trend. Statistically significant increases in rare squamous cell carcinoma of the forestomach were observed at both dosed groups, with a statistically significant trend. Additionally, statistically significant increases in rare exocrine adenomas of the pancreas were observed in the low-dose group.

Spontaneous occurrence of squamous cell carcinomas of the forestomach and exocrine adenomas in the pancreas were rare in males, based on data from male control Sprague-Dawley rats in long-term drinking water cancer bioassays performed by the Ramazzini Institute (initiated between 1986 and 1992)[9] and summarized by Gentry et al. (2024). No spontaneous carcinomas were observed in the forestomach of males (0/459, 6 studies). The spontaneous occurrence of pancreatic exocrine adenoma was 0.65% (3/459, 6 studies, ranging from 0–2%) (Gentry et al. 2024).

Table 14. Tumor incidence in male F_0 and F_1 Sprague-Dawley rats administered vinyl acetate in drinking water for 104 weeks (Minardi et al. 2002)

Study	Tumor site	Tumor type	Administered concentration in drinking water (ppm)			Trend test *p*-value
			0	1000	5000	
F_0	**Pancreas**	**Islet cell adenoma**	0/14	1/13	4/13*	< 0.05
F_1	**Oral cavity & lips**	**Squamous cell carcinoma**	2/107	0/83	13/53***	< 0.0001
	Fore-stomach	**Squamous cell carcinoma (r)**	0/107	6/83**	7/53***	< 0.01
	Pancreas	**Exocrine adenoma (r)**	0/107	5/83*	1/53	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Exact trend test conducted by OEHHA.
F_0, breeder animals; F_1, offspring; NS, not significant; (r), rare tumor, see text for details.

Non-neoplastic pathology findings

In F_1 males, statistically significant increases in squamous cell dysplasia[10] of the esophagus were observed in the high-dose group (control, 0/107; low-dose, 0/83; high-dose, 19/53, $p < 0.001$). Statistically significant increases in squamous cell dysplasia of the forestomach were observed in both dosed groups (control, 4/107; low-dose, 16/83, $p < 0.001$; high-dose, 13/53, $p < 0.001$). Aside from these findings, the authors reported that “there were no substantial differences between treated animals and controls in

[9] According to Gentry et al. (2024), the Minardi et al. (2002) studies were initiated in 1989.
[10] Dysplasia is a more advanced condition than hyperplasia and is considered by pathologists to be a preneoplastic lesion. Dysplasia is characterized by disordered growth and abnormal proliferation, and the cells have a distinctly abnormal and variable appearance (LaMorte 2016; Maronpot 2015). Squamous cell dysplasia is a form of epithelial proliferation (Leininger and Jokinen 1994).

mean body weight, survival, behavior, or treatment-related nononcological pathological changes."

Female F_0 and F_1 studies

The authors reported that there were no substantial differences between treated and control F_0 females or between treated and control F_1 females in mean body weight, survival, or behavior.

Table 15 presents tumor findings observed in females in the two studies.

In F_0 females, rare squamous cell carcinomas of the forestomach were observed in the high-dose group.

In F_1 females, a statistically significant increase in squamous cell carcinomas of the "oral cavity and lips" was observed at the high dose. Two rare squamous cell carcinomas of the tongue were observed at the high dose. There was a statistically significant increase in the incidence of rare forestomach squamous cell carcinoma at the high dose, with a dose-related trend. Additionally, a statistically significant increase in pheochromoblastoma of the adrenal gland was observed in the low-dose group.

Squamous cell carcinomas of the tongue and forestomach were rare in female Sprague-Dawley rats. In reference to the historical control data by the Ramazzini Institute, no spontaneous squamous cell carcinoma was observed in the tongue (0/165, 2 studies) or forestomach (0/415, 5 studies) of female Sprague-Dawley rats in drinking water studies initiated between 1986 and 1992 (Gentry et al. 2024).

Table 15. Tumor incidence in female F_0 and F_1 Sprague-Dawley rats administered vinyl acetate in drinking water for 104 weeks (Minardi et al. 2002)

Study	Tumor site	Tumor type	Administered concentration in drinking water (ppm)			Trend test *p*-value
			0	1000	5000	
F_0	**Forestomach**	**Squamous cell carcinoma (r)**	0/37	0/37	3/37	< 0.05
F_1	**Oral cavity & lips**	**Squamous cell carcinoma**	1/99	0/87	9/57***	< 0.0001
	Tongue	**Squamous cell carcinoma (r)**	0/99	0/87	2/57	NS
	Forestomach	**Squamous cell carcinoma (r)**	0/99	3/87	4/57*	< 0.05
	Adrenal gland	**Pheochromo-blastoma**	1/99	6/87*	3/57	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, *** $p < 0.001$
Exact trend test conducted by OEHHA.
F_0, breeder animals; F_1, offspring; NS, not significant; (r), rare tumor, see text for details.

Non-neoplastic pathology findings

Incidences of squamous cell dysplasia were observed in the tongue, esophagus, and forestomach of exposed females. In F_0 animals, statistically significant increases were observed at the high dose in the tongue (control, 0/37; low-dose, 3/37; high-dose, 7/37, $p < 0.01$), esophagus (control, 1/37; low-dose, 2/37; high-dose, 8/37, $p < 0.05$) and forestomach (control, 3/37; low-dose, 2/37; high-dose, 11/37, $p < 0.05$). In F_1 animals, statistically significant increases were observed at the high-dose in the tongue (control, 1/99; low-dose, 2/87; high-dose, 9/57, $p < 0.001$) and esophagus (control, 0/99; low-dose, 4/87; high-dose, 23/57, $p < 0.001$), and in both dosing groups in the forestomach (control, 4/99; low-dose, 14/87, $p < 0.01$; high-dose, 14/57, $p < 0.001$).

The authors noted that “there were no substantial differences between treated animals and controls in mean body weight, survival, behavior, or treatment-related nononcological pathological changes.”

4.1.6 104-week drinking water studies in male and female parental (F_0) and offspring (F_1) Wistar rats (Belpoggi et al. 2002)

This section discusses results from a set of four studies in Wistar rats (male F_0, male F_1, female F_0, and female F_1).

Male (n = 13–14) and female (n = 37) F_0 Wistar rats were administered 0, 1000, or 5000 ppm of vinyl acetate in drinking water starting from 17 weeks of age and continuing for 104 weeks. Male (n = 64–86) and female (n = 69–95) F_1 rats were exposed to 0, 1000, or 5000 ppm of vinyl acetate *in utero*, through lactation, and post weaning in drinking water (*ad libitum*) until 104 weeks of age. At the end of the treatment period all animals then received tap water until natural death. The average daily dose information (mg/kg-day) was not reported, and such information is unavailable because water consumption data were not provided. In these studies, fresh vinyl acetate solutions were prepared every day. The purity of vinyl acetate was >99%, with the following impurities reported: benzene (30–40 ppm), methyl and ethyl acetate (50 ppm), crotonaldehyde (6–16 ppm), acetaldehyde (2–11 ppm), and acetone (330–500 ppm).

In F_0 females, mean body weights were similar among control and both dosed groups. The survival of both dosed groups slightly decreased from the beginning of treatment to 104 weeks of age when compared to the control group. In F_1 females, a decrease in mean body weight was observed in the high-dose group when compared to the control group. The survival was similar among the treated groups and the control group.

OEHHA did not identify any appropriate historical control data that fulfill the following criteria: 1) using Wistar rats of similar origin (Ramazzini Institute), 2) by the oral routes, and 3) from studies initiated within ±3 years of the Belpoggi et al. (2002) studies.

Male F_0 and F_1 studies

In F_0 males, slight increases in mean body weight were observed in dosed animals compared to the control group. The mean survival in the high-dose group decreased from 72 to 120 weeks of age when compared to the control group. In F_1 males, there was a decrease in mean body weight in the high-dose group compared to the control group. A slight decrease in survival was observed in the low-dose group.

In F_0 males, no treatment-related tumor findings were observed.

Table 16 presents tumor findings observed in male F_1 Wistar rats.

In F_1 males, a statistically significant increase in squamous cell carcinoma of the “oral cavity and lips” was observed in the high-dose group compared to the control group. A statistically significant increase in pancreatic exocrine adenoma was observed in the low-dose group compared to the control group. In the adrenal gland, a statistically

significant increase in pheochromoblastoma was observed in the high-dose group, with a statistically significant trend.

OEHHA was not able to identify rare tumors in the Belpoggi et al. (2002) studies, because incidences of spontaneous tumors in male Wistar rats from this laboratory or other appropriate historical controls were not available.

Table 16. Tumor incidence in male F_1 Wistar rats administered vinyl acetate in drinking water for 104 weeks (Belpoggi et al. 2002)

Tumor site	Tumor type	Administered concentration in drinking water (ppm)			Trend test *p*-value
		0	1000	5000	
Oral cavity & lips	**Squamous cell carcinoma**	3/86	1/64	12/82**	< 0.001
Pharynx	**Carcinoma**	0/86	0/64	3/82	< 0.05
Esophagus	**Squamous cell carcinoma**	0/86	0/64	3/82	< 0.05
Forestomach	**Squamous cell carcinoma**	0/86	0/64	4/82	< 0.05
Pancreas	**Exocrine adenoma**	6/86	14/64**	4/82	NS
Adrenal gland	**Pheochromoblastoma**	0/86	1/64	5/82*	0.01

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$
Exact trend test conducted by OEHHA.
F_0, breeder animals; F_1, offspring; NS, not significant.

Non-neoplastic pathology findings

In F_1 males, a statistically significant increase in squamous cell dysplasia of the esophagus was observed in the high-dose group (control, 0/86; low-dose, 1/64; high-dose, 10/82, $p < 0.001$). The authors reported that “no treatment-related nononcological pathological changes were detected by gross inspection or histopathological examination.”

Female F_0 and F_1 studies

In F_0 females, mean body weights were similar among control and both dosed groups. The survival of both dosed groups of F_0 females was slightly decreased throughout the study when compared to the control group. In F_1 females, mean body weight was

decreased in the high-dose group when compared to controls. Survival was similar among treated and control F_1 females.

Table 17 presents tumor findings observed in female Wistar rats in the two studies.

In F_0 females, increases in lymphomas and leukemias of the hemolymphoreticular tissues were observed with a statistically significant trend. A statistically significant increase in pheochromocytoma of the adrenal gland was observed in the low-dose group compared to the control group. Fibrosarcomas of the uterus were observed in the high-dose group.

In F_1 females, statistically significant increases in lymphomas and leukemias of the hemolymphoreticular tissues, squamous cell carcinoma of the “oral cavity and lips”, squamous cell carcinoma of the tongue, and adenocarcinoma of the uterus were observed at the high dose, with a statistically significant trend for each of the tumor types.

OEHHA was not able to identify whether the tumors observed in the Belpoggi et al. (2002) studies were of the rare type, because incidences of spontaneous tumors in female Wistar rats from this laboratory or other appropriate historical controls were not available.

Table 17. Tumor incidence in female F_0 and F_1 Wistar rats administered vinyl acetate in drinking water for 104 weeks (Belpoggi et al. 2002)

Study	Tumor site	Tumor type	Administered concentration in drinking water (ppm)			Trend test *p*-value
			0	1000	5000	
F_0	Hemolympho-reticular tissues [1]	Lymphomas and leukemias	1/37	3/37	6/37	< 0.05
	Adrenal gland	Pheochromocytoma	5/37	14/37*	6/37	NS
	Uterus	Fibrosarcoma	0/37	0/37	3/37	< 0.05
F_1	Hemolympho-reticular tissues [1]	Lymphomas and leukemias	3/69	5/73	14/95*	< 0.01
	Oral cavity & lips	Squamous cell carcinoma	5/69	11/73	24/95**	< 0.01
	Tongue	Squamous cell carcinoma	0/69	0/73	6/95*	< 0.01
	Esophagus	Squamous cell carcinoma	0/69	1/73	4/95	< 0.05
	Forestomach	Squamous cell carcinoma	0/69	0/73	4/95	< 0.05
	Uterus	Adenocarcinoma	4/69	5/73	19/95**	0.001

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$
Exact trend test was conducted by OEHHA.
F_0, breeder animals; F_1, offspring; NS, not significant.
[1] Belpoggi et al. (2002) notes that these tissues include thymus, spleen, mediastinal and mesenteric lymph nodes.

Non-neoplastic pathology findings

In F_0 females, statistically significant increases in squamous cell dysplasia of the esophagus were observed at the high dose (control, 0/37; low-dose, 0/37; high-dose, 6/37, $p < 0.05$).

In F_1 females, statistically significant increases in squamous cell dysplasia were observed at the high dose in the oral cavity (control, 0/69; low-dose, 0/73; high-dose, 12/95, $p < 0.01$) and esophagus (control, 0/69; low-dose, 0/73; high-dose, 29/95, $p < 0.001$).

The authors reported that “no treatment-related nononcological pathological changes were detected by gross inspection or histopathological examination.”

4.2 Carcinogenicity Studies in Mice

4.2.1 104-week inhalation studies in male and female Crl:CD-1(ICR)BR mice (Bogdanffy et al. 1994a; Owen 1988)

104-week inhalation studies in male and female Crl:CD-1(ICR)BR mice were reported by Hazleton Laboratories UK (Owen 1988) and the data were published in a peer-reviewed article (Bogdanffy et al. 1994a).

45-day-old male and female Crl:CD-1(ICR)BR mice, an outbred strain derived from Swiss mice, were administered 0, 50, 200, 600 ppm vinyl acetate by inhalation (6 hours per day, 5 days per week, except two holidays per year) for 104 weeks. In each study, each experimental group was comprised of 60 animals. Average daily doses were calculated to be 0, 37, 148, 443 mg/kg-day for males, and 0, 37, 148, and 445 mg/kg-day for females. The purity of vinyl acetate used in the studies was > 99%, with some impurities reported, including acetic acid (≤10 ppm) and acetaldehyde (≤ 65 ppm). Similar to the studies in rats (Bogdanffy et al. 1994a; Owen 1988), the histological examination of tissues (other than the respiratory tract) in the low- and mid-dose groups may not have been adequate (see discussion in Section 4.1.1).

Males

In males, the mortality in the dosed groups was comparable to that of the control group. The average body weight in the 600-ppm group was statistically significantly lower than that of the controls.

No treatment-related tumor findings were observed in male Crl:CD-1(ICR)BR mice in the 104-week inhalation studies.

Non-neoplastic pathology findings

A variety of non-neoplastic findings in the nasal cavity and trachea of male mice were reported (Table 18). Note that in male mice the respiratory epithelium was affected (e.g., squamous metaplasia at the naso/maxilloturbinate region), in contrast to the Bogdanffy et al. (1994a) rat studies where effects on the nasal cavity were limited to the olfactory epithelium.

Table 18. Non-neoplastic lesions in male mice (Bogdanffy et al. 1994a)

Tissue site	Non-neoplastic finding and severity (if applicable)	Administered concentration in air (ppm)			
		0	50	200	600
Nasal cavity	**Mucosal inflammatory infiltrate**	1/52	0/48	0/53	12/50***
	Submucosal gland hyperplasia				
	Slight	3/52	3/48	28/53***	25/50***
	Moderate	0/52	0/48	8/53**	15/50***
	Olfactory epithelial atrophy (mainly dorsal meatus)				
	Moderate	0/52	0/48	28/53***	2/50
	Olfactory epithelial atrophy (widespread)				
	Moderate	1/52	0/48	8/53*	5/50
	Severe	0/52	0/48	4/53	39/50***
	Squamous metaplasia at the naso/maxillo-turbinate region				
	Slight	1/52	1/48	2/53	13/50***
	Moderate	0/52	1/48	0/53	11/50***
	Replacement of the olfactory epithelium by respiratory epithelium				
	Slight	0/52	0/48	5/53*	11/50***
Trachea	**Epithelial hyperplasia**	0/49	0/46	2/51	19/48***

Incidences were reported by Bogdanffy et al. (1994a) and the denominators represent the number of animals from which this tissue was examined microscopically. Treatment group incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

Females

In females, the mortality in the dosed groups was comparable to that of the control group. The average body weight in the 600-ppm group was statistically significantly lower than that of the controls.

No treatment-related tumor findings were observed in female Crl:CD-1(ICR)BR mice in the 104-week inhalation studies.

Non-neoplastic pathology findings

A variety of non-neoplastic findings in the nasal cavity and trachea of female mice were reported (Table 19). Note that in female mice, the respiratory epithelium was affected (e.g., squamous metaplasia at the naso/maxilloturbinate region), in contrast to the Bogdanffy et al. (1994a) rat studies where effects on the nasal cavity were limited to the olfactory epithelium.

Table 19. Non-neoplastic lesions in female mice (Bogdanffy et al. 1994a)

Tissue site	Non-neoplastic finding and severity (if applicable)	Administered concentration in air (ppm)			
		0	50	200	600
Nasal cavity	**Submucosal gland hyperplasia**				
	Slight	2/56	5/57	42/55***	35/51***
	Moderate	0/56	0/57	7/55**	13/51***
	Olfactory epithelial atrophy (mainly dorsal meatus)				
	Slight	2/56	4/57	8/55*	0/51
	Moderate	0/56	0/57	26/55***	0/51
	Olfactory epithelial atrophy (widespread)				
	Moderate	0/56	0/57	12/55***	5/51*
	Severe	0/56	0/57	2/55	45/51***
	Squamous metaplasia at the naso/maxillo-turbinate region				
	Slight	4/56	2/57	0/55	13/51**
	Moderate	0/56	0/57	0/55	6/51*
	Replacement of olfactory epithelium by respiratory epithelium				
	Slight	0/56	0/57	15/55***	10/51***
	moderate	0/56	1/57	5/55*	10/51***
Tracheal	**Epithelial hyperplasia**	1/55	1/56	0/52	11/48***

Incidences were reported by Bogdanffy et al. (1994a) and the denominators represent the number of animals from which this tissue was examined microscopically. Treatment group incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

4.2.2 104-week drinking water studies in male and female Crj:BDF1 mice (JBRC 1995; Umeda et al. 2004)

104-week drinking water studies in male and female Crj:BDF1 mice were reported by The Japan Biological Information Research Center (JBRC 1995) and the data were later published in a peer-reviewed article (Umeda et al. 2004).

Male and female Crj:BDF1 mice at 6 weeks of age (50 animals per group) were administered 0, 400, 2000 or 10000 ppm vinyl acetate (> 98% purity) in drinking water for 104 weeks. Necropsy was performed on all animals. All major organs were examined for histopathology. Umeda et al. (2004) reported that average daily intakes of vinyl acetate were 0, 42, 202, and 989 mg/kg-day for males, and 0, 63, 301, and 1418 mg/kg-day for females in the two-year studies. Vinyl acetate solutions were prepared twice a week during the studies. The authors observed that the concentrations of vinyl acetate in the administered solutions decreased to 86-96% of the starting concentrations due to evaporation four days after preparation, likely resulting in lower doses than intended. Additionally, they noted that concentrations of acetic acid in the prepared solutions increased with higher concentrations of vinyl acetate. Acetic acid concentrations were 9.2 ppm for the 400-ppm solution, 47 ppm for the 2000-ppm solution, and 263 ppm for the 10000-ppm solution.

Males

In males, there was no significant difference in survival between the treated groups and the controls. The average body weight in the 10000 ppm (high-dose) group was statistically significantly lower than the control group ($p < 0.01$, reported by the authors) at the end of the study.

Tumors observed in the 104-week drinking water study in male mice are presented in Table 20. In the oral cavity and the forestomach, statistically significant increases in rare squamous cell carcinoma, and rare squamous cell papilloma and carcinoma combined were observed at the high dose. This study defined oral cavity tumors as tumors of the hard palate, buccal mucosa, gingiva, and lip mucosa. In the esophagus, rare squamous cell carcinomas were statistically significantly increased at the high dose. Additionally, two rare squamous cell papillomas of the larynx were observed at the high dose.

Spontaneous occurrence of squamous cell papilloma or carcinoma is rare in the upper gastrointestinal tract of this strain of mouse. No spontaneous squamous cell carcinoma of the oral cavity (0/996), esophagus (0/996) or larynx (0/996) was observed in male Crj:BDF1 mice among historical studies conducted in this laboratory from 1987 to 2002 (Umeda et al. 2004). Spontaneous occurrence of squamous cell tumors of the forestomach is also rare, with a historical rate in this laboratory of 0.2% for papilloma (2/996), and 0% for carcinoma (0/996) (Umeda et al. 2004).

Table 20. Incidence of upper gastrointestinal tract tumors in male Crj:BDF1 mice administered vinyl acetate in drinking water for 104 weeks (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration in drinking water (ppm)				Trend test p-value [1]
		0	400	2000	10000	
Oral cavity (including lip mucosa)	**Squamous cell papilloma (r)**	0/50	0/50	0/50	4/50	< 0.01
	Squamous cell carcinoma (r)	0/50	0/50	0/50	13/50***	< 0.0001
	Combined (r)	0/50	0/50	0/50	16/50***	< 0.0001
Larynx	**Squamous cell papilloma (r)**	0/50	0/50	0/50	2/50	NS
Esophagus	**Squamous cell carcinoma (r)**	0/50	0/50	0/50	7/50**	< 0.0001
Forestomach	**Squamous cell papilloma (r)**	0/50	0/50	0/50	2/50	NS
	Squamous cell carcinoma (r)	1/50	0/50	0/50	7/50*	< 0.001
	Combined (r)	1/50	0/50	0/50	9/50**	< 0.0001

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$,
[1] Exact trend test conducted by OEHHA. JBRC (1995) performed the Cochran-Armitage trend test and three types of Peto trend tests, namely standard method, prevalence method, and combined analysis. Standard method was referred to as “death analysis”, prevalence method was referred to as “incidental tumor test”, and the combined analysis was referred to as “death analysis + incidental tumor test”. These trend test results are not presented in this document because all of the tumor incidence increases were seen in the high-dose group only.
NS, not significant; (r) denotes a rare tumor, see text for details.

Non-neoplastic pathology findings

A variety of non-neoplastic lesions in the upper gastrointestinal tract of male mice were reported, including basal cell activation, squamous cell hyperplasia, and epithelial dysplasia in the oral cavity, larynx, esophagus, and forestomach, some of which were statistically significantly increased compared to controls (Table 21). JBRC (1995) considered the squamous cell hyperplasia, basal cell activation, and epithelial dysplasia to be growth-related cell changes and lesions that represent early stages of cancer. JBRC also noted “epithelial dysplasia represents a precancerous lesion that contributes greatly to cell malignancy”.

Table 21. Non-neoplastic lesions in the upper gastrointestinal tract in male mice (JBRC 1995; Umeda et al. 2004)

Non-neoplastic finding	Administered concentration in drinking water (ppm)			
	0	400	2000	10000
Oral cavity basal cell activation	0/50	0/50	1/50	18/50***
Oral cavity squamous cell hyperplasia	0/50	0/50	2/50	13/50***
Oral cavity epithelial dysplasia	0/50	0/50	0/50	24/50***
Larynx basal cell activation	0/50	0/50	0/50	3/50
Larynx squamous cell hyperplasia	0/50	0/50	0/50	1/50
Larynx epithelial dysplasia	0/50	0/50	0/50	2/50
Esophagus basal cell activation	0/50	0/50	0/50	9/50**
Esophagus squamous cell hyperplasia	0/50	0/50	0/50	2/50
Esophagus epithelial dysplasia	0/50	0/50	0/50	2/50
Forestomach basal cell activation	0/50	0/50	0/50	1/50
Forestomach squamous cell hyperplasia	0/50	0/50	0/50	3/50
Forestomach epithelial dysplasia	0/50	0/50	0/50	1/50

Treatment group incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): ** $p < 0.01$, *** $p < 0.001$.

Females

In females, there was no significant difference in survival between the treated groups and the controls. The average body weight in the 10000 ppm (high-dose) group was statistically significantly lower than the control group ($p < 0.01$, reported by the authors) at the end of the study.

Tumors observed in the 104-week drinking water study in female mice are presented in Table 22. In the oral cavity, statistically significantly increases in rare squamous cell carcinoma, and squamous cell papilloma and carcinoma combined were observed at the high dose. In the forestomach, one rare squamous cell papilloma and three rare squamous cell carcinomas were observed at the high dose. Additionally, a statistically

significant increase in malignant lymphoma of the spleen was observed in the low-dose (400 ppm) group.

Spontaneous occurrence of squamous cell tumors of the oral cavity was rare, with a rate of 0.1% for papilloma (1/998), and 0% for carcinoma (0/998) in female Crj:BDF1 mice among historical studies conducted in this laboratory from 1987 to 2002 (Umeda et al. 2004). The occurrence of spontaneous squamous cell tumors of the forestomach was also rare in this laboratory, with a rate of 0.4% for papilloma (4/998) and 0.2% for carcinoma (2/998) (Umeda et al. 2004).

Table 22. Incidence of tumors in female Crj:BDF1 mice administered vinyl acetate in drinking water for 104 weeks (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration in drinking water (ppm)				Trend test p-value [1]
		0	400	2000	10000	
Oral cavity (including lip mucosa)	Squamous cell papilloma (r)	0/50	0/50	0/50	3/50	< 0.05
	Squamous cell carcinoma (r)	0/50	0/50	0/50	15/50***	< 0.0001
	Combined (r)	0/50	0/50	0/50	18/50***	< 0.0001
Forestomach	Squamous cell papilloma (r)	0/50	0/50	0/50	1/50	NS
	Squamous cell carcinoma (r)	0/50	0/50	0/50	3/50	< 0.05
	Combined (r)	0/50	0/50	0/50	4/50	< 0.01
Spleen	Malignant lymphoma	0/50	5/50*	1/50	1/50	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, *** $p < 0.001$,
[1] Exact trend test conducted by OEHHA. For the oral cavity and forestomach tumors, JBRC (1995) performed the Cochran-Armitage trend test and three types of Peto trend tests, namely standard method, prevalence method, and combined analysis. Standard method was referred to as “death analysis”, prevalence method was referred to as “incidental tumor test”, and the combined analysis was referred to as “death analysis + incidental tumor test”. These trend test results are not presented in this document because all of the oral cavity and forestomach tumor incidence increases were seen in the high-dose group only.
NS, not significant; (r) denotes a rare tumor, see text for details.

Non-neoplastic pathology findings

A variety of non-neoplastic lesions in the upper gastrointestinal tract of female mice were reported, including basal cell activation, squamous cell hyperplasia, and epithelial dysplasia in the oral cavity, larynx, esophagus, or forestomach, several of which were statistically significantly increased compared to controls (Table 23). JBRC (1995) considered the squamous cell hyperplasia and basal cell activation to be growth-related cell changes and lesions that represent early stages of cancer. JBRC also noted "epithelial dysplasia represents a precancerous lesion that contributes greatly to cell malignancy".

Table 23. Non-neoplastic lesions of the upper gastrointestinal tract in female mice (JBRC 1995; Umeda et al. 2004)

Non-neoplastic finding	Administered concentration in drinking water (ppm)			
	0	400	2000	10000
Oral cavity basal cell activation	0/50	0/50	1/50	17/49***
Oral cavity squamous cell hyperplasia	0/50	0/50	1/50	6/49*
Oral cavity epithelial dysplasia	0/50	0/50	0/50	17/49***
Larynx basal cell activation	0/50	0/50	0/50	6/49*
Larynx epithelial dysplasia	0/50	0/50	0/50	3/49
Esophagus basal cell activation	0/50	0/50	0/50	15/49***
Esophagus squamous cell hyperplasia	0/50	0/50	0/50	2/49
Esophagus epithelial dysplasia	0/50	0/50	0/50	7/49**
Forestomach basal cell activation	0/50	0/50	0/50	1/49
Forestomach squamous cell hyperplasia	0/50	2/50	0/50	4/49

Treatment group incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

4.2.3 78-week drinking water studies in male and female parental (F_0) and offspring (F_1) Swiss mice (Maltoni et al. 1997)

This section discusses results from a set of four studies in Swiss mice (male F_0, male F_1, female F_0, and female F_1).

Male (n = 13–14) and female (n = 37) F_0 Swiss mice were administered 0, 1000, 5000 ppm vinyl acetate in drinking water starting from 17 weeks of age for 78 weeks. Male (n = 37–49) and female (n = 44–48) F_1 mice were exposed to 0, 1000, or 5000 ppm vinyl acetate starting *in utero* on gestation day 12, through lactation, and post-weaning in drinking water *ad libitum* until 78 weeks of age. At the end of the treatment period all animals then received tap water until natural death. In these studies, fresh vinyl acetate solutions were prepared every day. The purity of vinyl acetate was > 99%, with several impurities reported: benzene (30–45 ppm), methyl and ethyl acetate (50 ppm), crotonaldehyde (6–16 ppm), acetaldehyde (2–11 ppm), and acetone (330–500 ppm). The average daily dose (mg/kg-day) was not reported, and such information is unavailable because water consumption data were not provided.

OEHHA did not identify any appropriate historical control data that fulfill the following criteria: 1) using Swiss mice of similar origin (e.g., Ramazzini Institute), 2) by the oral routes, and 3) from Ramazzini Institute studies initiated within ±3 years of the Maltoni et al. (1997) studies.

Male F_0 and F_1 studies

In F_0 males, there were no differences in mean body weight in dosed groups and the control group. The survival rates of both dosed groups were decreased compared to controls from the start of the experiment (17 weeks of age) to 72 weeks of age. Survival in the high-dose group was increased compared to controls from 72 to 120 weeks of age. In F_1 males, slight decreases in mean body weight were observed in both dosed groups compared to that of the control group. An increase in survival was observed at the high dose compared to controls.

No treatment related tumors were observed in F_0 males treated with vinyl acetate for 78 weeks.

In F_1 males, tumors observed in the oral cavity[11], tongue, esophagus, and forestomach are presented in Table 24. Statistically significant increases in squamous cell carcinoma of oral cavity, squamous cell carcinoma of the esophagus, and acanthoma of the forestomach were observed at the high dose. There were statistically significant dose-related trends for forestomach acanthoma and squamous cell carcinoma of the tongue.

[11] This publication did not specify whether oral cavity tumors include tumors of the lips.

Table 24. Tumor incidence in male F_1 Swiss mice administered vinyl acetate in drinking water for 78 weeks (Maltoni et al. 1997)

Tumor site	Tumor type	Administered concentration in drinking water (ppm)			Trend test *p*-value
		0	1000	5000	
Oral cavity	**Squamous cell carcinoma**	0/38	0/37	10/49**	< 0.0001
Tongue	**Squamous cell carcinoma**	1/38	0/37	7/49	< 0.01
Esophagus	**Squamous cell carcinoma**	0/38	0/37	12/49***	< 0.0001
Forestomach	**Acanthoma**	0/38	1/37	8/49**	< 0.01

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined at the end of the study.
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): ** $p < 0.01$, *** $p < 0.001$
Exact trend test conducted by OEHHA.

Non-neoplastic pathology findings

In F_0 males, a statistically significant increase in squamous cell dysplasia of the esophagus (control, 0/14; low-dose, 0/13; high-dose, 4/13, $p < 0.05$) was observed at the high dose.

In F_1 males, increases that did not reach statistical significance were observed in squamous cell dysplasia of the tongue (control, 0/38; low-dose, 0/37; high-dose, 4/49), esophagus (control, 0/38; low-dose, 0/37; high-dose, 4/49), forestomach (control, 0/38; low-dose, 0/37; high-dose, 1/49), and Zymbal gland (control, 2/38; low-dose, 0/37; high-dose, 4/49) at the high dose.

The authors reported that “no treatment-related nononcological pathological changes were detected by gross inspection and histological examination.”

Female F_0 and F_1 studies

In F_0 females, there were no differences in mean body weight in dosed groups and the control group. A slight decrease in survival was observed at the low dose when compared to that of the control group. In F_1 females, decreases in mean body weight were observed in both dosed groups compared to the control group. An increase in survival was observed at the high dose.

Table 25 presents tumor findings observed in female Swiss mice in the two studies. In F_0 females, statistically significant increases in squamous cell carcinoma of esophagus

and acanthoma of the forestomach were observed at the high dose. Three squamous cell carcinomas of the forestomach were also observed at the high dose. In F_1 females, statistically significant increases in squamous cell carcinomas of the oral cavity, tongue, esophagus, and forestomach, and acanthomas of the forestomach were observed at the high dose. Statistically significant dose-related trends for leiomyosarcoma of the uterus, adenoma of the lung, and carcinoma of the Zymbal gland were also observed.

Table 25. Tumor incidence in female F_0 and F_1 Swiss mice administered vinyl acetate in drinking water for 78 weeks (Maltoni et al. 1997)

Study	Tumor site	Tumor type	Administered concentration in drinking water (ppm)			Trend test p-value
			0	1000	5000	
F_0	Esophagus	Squamous cell carcinoma	0/37	0/37	6/37*	0.0010
	Forestomach	Acanthoma	0/37	0/37	5/37*	< 0.01
		Squamous cell carcinoma	0/37	0/37	3/37	< 0.05
F_1	Oral cavity	Squamous cell carcinoma	0/48	0/44	9/48**	< 0.0001
	Tongue	Squamous cell carcinoma	0/48	0/44	12/48***	< 0.0001
	Esophagus	Acanthoma	0/48	0/44	3/48	< 0.05
		Squamous cell carcinoma	0/48	0/44	18/48***	< 0.0001
	Forestomach	Acanthoma	0/48	0/44	11/48***	< 0.0001
		Squamous cell carcinoma	0/48	0/44	7/48**	< 0.001
	Uterus	Leiomyosarcoma	0/48	2/44	4/48	< 0.05
	Lung	Adenoma	6/48	3/44	11/48	< 0.05
	Mammary gland	Liposarcoma	0/48	0/44	3/48	< 0.05
	Zymbal gland	Carcinoma	0/48	2/44	4/48	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals examined. Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Exact trend test conducted by OEHHA.

Non-neoplastic pathology findings

In F_0 females, statistically significant increases were observed in squamous cell dysplasia of the esophagus (control, 0/37; low-dose, 0/37; high-dose, 6/37, $p < 0.05$) at the high dose. Increases that did not reach statistical significance were observed in squamous cell dysplasia of the tongue (control, 0/37; low-dose, 0/37; high-dose, 3/37), and Zymbal gland (control, 1/37; low-dose, 3/37; high-dose, 6/37).

In F_1 females, statistically significant increases in squamous cell dysplasia of the tongue (control, 0/48; low-dose, 1/44; high-dose, 7/48, $p < 0.01$), esophagus (control, 0/48; low-dose, 0/44; high-dose, 7/48, $p < 0.01$), and Zymbal gland (control, 3/48; low-dose, 2/44; high-dose, 11/48, $p < 0.05$) were observed at the high dose.

The authors reported that “no treatment-related nononcological pathological changes were detected by gross inspection and histological examination.”

4.3 Summary of animal carcinogenicity studies

4.3.1. Summary of animal tumor findings of vinyl acetate, organized by species and strain

Carcinogenicity studies of vinyl acetate have been conducted in male and female Sprague-Dawley (SD) rats, SD derived Crl:CD(SD)BR rats, Fischer 344 rats, F344/DuCrj rats, Wistar rats, Swiss mice, Swiss derived Crl:CD-1(ICR)BR mice, and Crj:BDF1 mice.

Statistically significant tumor findings from vinyl acetate studies in rats and mice, along with biologically relevant rare tumors, are shown in Table 26. In addition, a bulleted summary of the animal tumor findings is presented by species, strain and sex. The statistically significant increases in the following summary refer to Fisher pairwise comparison with controls.

Tumors in male SD rats

• In the 104-week drinking water study in vinyl acetate treated parental (F_0) male SD rats, the incidence of pancreatic islet cell adenomas was significantly increased in the high-dose (5000 ppm) group, with a significant dose-related trend (Minardi et al. 2002).

• In the 104-week drinking water study in vinyl acetate treated offspring (F_1) male SD rats, the incidence of oral cavity and lips squamous cell carcinoma was significantly increased in the high-dose (5000 ppm) group, with a significant dose-related trend. The incidence of rare forestomach squamous cell carcinoma was significantly increased in the low- (1000 ppm) and high-dose (5000 ppm) groups, with a significant dose-related trend. The incidence of rare pancreatic exocrine adenoma was significantly increased in

the low-dose group, with no adenomas in the control and one rare adenoma in the high-dose group (Minardi et al. 2002).

Tumors in female SD rats

• In the 104-week drinking water study in vinyl acetate treated F_0 female SD rats, there was a statistically significant dose-related trend in the incidences of rare forestomach squamous cell carcinoma (Minardi et al. 2002).

• In the 104-week drinking water study in vinyl acetate treated F_1 female SD rats, the incidences of squamous cell carcinoma of the oral cavity and lips and of the forestomach (rare) were each significantly increased in the high-dose (5000 ppm) group, with significant dose-related trends. The incidence of adrenal pheochromoblastoma was significantly increased in the low-dose (1000 ppm) group. Two rare squamous cell carcinomas of the tongue were observed in the high-dose group (Minardi et al. 2002).

Tumors in male Crl:CD(SD)BR rats

• In the 104-week inhalation study in vinyl acetate treated male Crl:CD(SD)BR rats, there was a significant dose-related trend in the incidences of rare nasal squamous cell papilloma. The incidence of total rare nasal tumors (squamous cell papilloma, carcinoma, and carcinoma *in situ* combined) was significantly increased in the high-dose (600 ppm) group, with a significant dose-related trend (Bogdanffy et al. 1994a; Owen 1988).

Tumors in female Crl:CD(SD)BR rats

• In the 104-week inhalation study in vinyl acetate treated female Crl:CD(SD)BR rats, there was a statistically significant dose-related trend in the incidences of rare nasal cavity squamous cell carcinoma. One rare squamous cell carcinoma of the larynx was observed in the high-dose (600 ppm) group (Bogdanffy et al. 1994a; Owen 1988).

Tumors in male F344/DuCrj rats

• In the 104-week drinking water study in vinyl acetate treated male F344/DuCrj rats, the incidences of rare oral cavity (including lip mucosa) squamous cell carcinoma, and rare papilloma and carcinoma combined were significantly increased in the high-dose (10000 ppm) group, with a significant dose-related trend. Two rare oral cavity (including lip mucosa) squamous cell papillomas were observed in the high-dose group. There was a statistically significant dose-related trend in the incidences of testicular interstitial cell tumors (JBRC 1995; Umeda et al. 2004).

Tumors in female Fischer 344 and F344/DuCrj rats

• In the 100-week drinking water study in vinyl acetate treated female Fischer 344 rats, the incidence of liver hepatocellular adenoma was significantly increased in the high-

dose (2500 ppm) group, with a significant dose-related trend. In the uterus, there was a statistically significant dose-related trend in the incidences of rare adenocarcinoma. The incidence of endometrial stromal polyps was significantly increased in the high-dose group, with a significant dose-related trend. In the thyroid gland, the incidence of C-cell adenoma was significantly increased in the high-dose group with a significant dose-related trend, and there was a statistically significant dose-related trend in the incidences of C-cell adenoma and carcinoma combined. In the pituitary gland, there was a statistically significant dose-related trend in the incidences of adenoma (EPL 1982; Lijinsky and Reuber 1983).

• In the 104-week drinking water study in vinyl acetate treated female F344/DuCrj rats, there was a statistically significant dose-related trend in the incidences of rare oral cavity (including lip mucosa) squamous cell carcinoma. The incidences of thyroid C-cell adenomas, and C-cell adenoma and carcinoma combined were significantly increased in the mid-dose (2000 ppm) group. There was a statistically significant dose-related trend in the incidences of mammary gland adenocarcinoma (JBRC 1995; Umeda et al. 2004).

Tumors in male Wistar rats

• In the 104-week drinking water study in vinyl acetate treated F_1 male Wistar rats, the incidence of squamous cell carcinoma of the oral cavity and lips was significantly increased in the high-dose (5000 ppm) group, with a significant dose-related trend. The incidence of pancreatic exocrine adenoma was significantly increased in the low-dose (1000 ppm) group. The incidence of adrenal gland pheochromoblastoma was significantly increased in the high-dose group with a significant dose-related trend. There was a statistically significant dose-related trend in the incidences of pharynx carcinoma, squamous cell carcinomas of the esophagus, and squamous cell carcinoma of the forestomach (Belpoggi et al. 2002).

Tumors in female Wistar rats

• In the 104-week drinking water study in vinyl acetate treated F_0 female Wistar rats, there was a statistically significant dose-related trend in the incidences of lymphomas and leukemias of hemolymphoreticular tissues. The incidence of adrenal gland pheochromocytoma was significantly increased in the low-dose (1000 ppm) group. There was a statistically significant dose-related trend in the incidences of uterine fibrosarcoma (Belpoggi et al. 2002).

• In the 104-week drinking water study in vinyl acetate treated F_1 female Wistar rats, the incidence of lymphomas and leukemias of hemolymphoreticular tissues was significantly increased in the high-dose (5000 ppm) group, with a significant dose-related trend. The incidences of squamous cell carcinomas of the oral cavity and lips and of the tongue were significantly increased in the high-dose group, with significant

dose-related trends. There were statistically significant dose-related trends in the incidences of squamous cell carcinoma of the esophagus and of the forestomach. The incidence of uterine adenocarcinoma was significantly increased in the high-dose group, with a significant dose-related trend (Belpoggi et al. 2002).

Tumors in male Swiss mice

• In the 78-week drinking water study in vinyl acetate treated F_1 male Swiss mice, the incidences of squamous cell carcinoma of the oral cavity and of the esophagus were each significantly increased in the high-dose (5000 ppm) group, with significant dose-related trends. There was a statistically significant dose-related trend in the incidences of squamous cell carcinoma of the tongue. The incidence of forestomach acanthoma was significantly increased in the high-dose group, with a significant dose-related trend (Maltoni et al. 1997).

Tumors in female Swiss mice

• In the 78-week drinking water study in vinyl acetate treated F_0 female Swiss mice, the incidences of squamous cell carcinoma of the esophagus and forestomach acanthoma were significantly increased in the high-dose (5000 ppm) group, with significant dose-related trends. There was a statistically significant dose-related trend in the incidences of squamous cell carcinoma of the forestomach (Maltoni et al. 1997).

• In the 78-week drinking water study in vinyl acetate treated F_1 female Swiss mice, the incidences of squamous cell carcinoma of the oral cavity, tongue, esophagus, and forestomach were each significantly increased in the high-dose (5000 ppm) group, with significant dose-related trends. The incidence of forestomach acanthoma was significantly increased in the high-dose group with a significant dose-related trend. There were statistically significant dose-related trends in the incidences of esophageal acanthoma, uterine leiomyosarcoma, lung adenoma, mammary gland liposarcoma, and Zymbal gland carcinoma (Maltoni et al. 1997).

Tumors in male Crj:BDF1 mice

• In the 104-week drinking water study in vinyl acetate treated male Crj:BDF1 mice, the incidences of squamous cell carcinoma, and papilloma and carcinoma combined of the oral cavity (including lip mucosa; all rare tumors) and of the forestomach (rare) were significantly increased in the high-dose (10000 ppm) group, with significant dose-related trends. There was a statistically significant dose-related trend in the incidences of rare squamous cell papilloma of the oral cavity (including lip mucosa). Two rare squamous cell papillomas were observed in the high-dose group in both the larynx and the forestomach. The incidence of rare squamous cell carcinoma of the esophagus was significantly increased in the high-dose group, with a significant dose-related trend (JBRC 1995; Umeda et al. 2004).

Tumors in female Crj:BDF1 mice

• In the 104-week drinking water study in vinyl acetate treated female Crj:BDF1 mice, the incidences of squamous cell carcinoma, and papilloma and carcinoma combined of the oral cavity (including lip mucosa; all rare tumors) were significantly increased in the high-dose (10000 ppm) group, with significant dose-related trends. There was a statistically significant dose-related trend in the incidences of rare squamous cell papilloma of the oral cavity (including lip mucosa). There was a statistically significant dose-related trend in the incidences of squamous cell carcinoma, and papilloma and carcinoma combined of the forestomach (rare tumors). One rare squamous cell papilloma of the forestomach was observed in the high-dose group. The incidence of malignant lymphoma of the spleen was significantly increased in the low-dose (400 ppm) group (JBRC 1995; Umeda et al. 2004).

Table 26. Summary of tumor findings from animal studies of vinyl acetate, with statistically significant findings in bold

Species & strain / System	Rats					Mice[1]	
	Sprague-Dawley (SD) (Minardi et al. 2002)	**SD derived Crl:CD(SD)BR** (Bogdanffy et al. 1994a; Owen 1988)	**Fischer 344** (EPL 1982; Lijinsky and Reuber 1983)	**F344/DuCrj** (JBRC 1995; Umeda et al. 2004)	**Wistar** (Belpoggi et al. 2002)	**Swiss** (Maltoni et al. 1997)	**Crj:BDF1** (JBRC 1995; Umeda et al. 2004)
Respiratory		**Nasal cavity SCP (M)[3],** SCC (M[3], F[2,3]), carcinoma *in situ* (M)[3], **SCP, SCC and carcinoma *in situ* combined (M)[3]** Larynx SCC (F)[3]			Pharynx carcinoma (M)[2]	Lung adenoma (F)[2]	Larynx SCC (M)[3]
Digestive	**Oral cavity and lips SCC (M, F)** Tongue SCC (F)[3] **Forestomach SCC (M, F)[3]** **Pancreatic Islet cell adenoma (M), Pancreatic exocrine adenoma (M)[3]**		**Liver hepatocellular adenoma (F)**	**Oral cavity and lips SCC (M, F)[3], SCC and SCP combined (M)[3]**, SCP (M)[3]	**Oral cavity and lips SCC (M, F)** **Tongue SCC (F)** **Esophagus SCC** (M[2], **F**) Forestomach SCC (M, F)[2] **Pancreatic exocrine adenoma (M)**	**Oral cavity SCC (M, F)** **Tongue SCC** (M[2], **F**) **Esophagus SCC (M, F),** Esophagus acanthoma (F)[2] **Forestomach SCC (F), Forestomach acanthoma (M, F)**	**Oral cavity and lips SCC (M, F)[3],** SCP (M, F)[2,3], **and SCC and SCP combined (M, F)[3]** **Esophagus SCC (M)[3]** **Forestomach SCC** (**M[3],** F[2,3]), SCP (M, F)[3], **SCC and SCP combined** (**M[3],** F[2,3])

Species & strain / System	Rats					Mice[1]	
	Sprague-Dawley (SD) (Minardi et al. 2002)	**SD derived Crl:CD(SD)BR** (Bogdanffy et al. 1994a; Owen 1988)	**Fischer 344** (EPL 1982; Lijinsky and Reuber 1983)	**F344/DuCrj** (JBRC 1995; Umeda et al. 2004)	**Wistar** (Belpoggi et al. 2002)	**Swiss** (Maltoni et al. 1997)	**Crj:BDF1** (JBRC 1995; Umeda et al. 2004)
Endocrine	**Adrenal gland pheochromoblastoma (F)**		**Pituitary adenoma (F)** **Thyroid C-cell tumors (adenoma, adenoma and carcinoma combined) (F)**	**Thyroid C-cell tumors (adenoma, adenoma and carcinoma combined) (F)**	**Adrenal gland pheochromoblastoma (M), pheochromocytoma (F)**		
Reproductive			**Uterine adenocarcinoma (F)[3], Uterine endometrial stromal polyp (F)**	**Testicular interstitial cell tumors (M)**	**Uterine adenocarcinoma (F)**, Uterine fibrosarcoma (F)[2]	**Uterine leiomyosarcoma (F)**	
Immune					**Lymphomas and leukemias of the hemolymphoreticular tissues (F)**		**Malignant lymphoma of the spleen (F)**
Auditory						**Zymbal gland carcinoma (F)**	
Integumentary				Mammary gland adenocarcinoma (F)[2]		Mammary gland liposarcoma (F)[2]	

M, male; F, female; SCC, squamous cell carcinoma; SCP, squamous cell papilloma

[1] The 104-week inhalation studies in male and female Crl:CD-1(ICR)BR mice (Bogdanffy et al. 1994a; Owen 1988) did not identify any treatment related tumors and are not included in this table.

[2] Tumor incidences with an apparent statistically significant trend, driven by increases (statistically non-significant) of tumors only at the high-dose in comparison to controls. These findings are not in bold.

[3] Rare tumor

4.3.2. Summary of tumor findings from animal carcinogenicity studies of acetaldehyde

As noted at the beginning of section 4, the vinyl acetate metabolite acetaldehyde is a "Group 2B" carcinogen (possibly carcinogenic to humans) by IARC and "Reasonably anticipated to be a human carcinogen" by the NTP's Report on Carcinogens. Both classifications are based on sufficient evidence of carcinogenicity in experimental animals. The animal tumor findings for acetaldehyde are summarized as follows:

- IARC (1999): "Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and in hamsters by inhalation exposure and by intratracheal instillation. It produced tumours of the respiratory tract following inhalation, particularly adenocarcinomas and squamous-cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters. In hamsters, it did not cause an increased incidence of tumours following intratracheal instillation. Inhalation of acetaldehyde enhanced the incidence of respiratory-tract tumours produced by intratracheal instillation of benzo[a]pyrene."
- NTP (2021): Findings from studies in rats published subsequent to the IARC 1999 review: "Since acetaldehyde was listed in the Sixth Annual Report on Carcinogens, an additional study in rats has been identified. Administration of acetaldehyde in drinking water increased the incidences of hemolymphoreticular cancer (leukemia and lymphoma combined), benign tumors of the pancreas (islet-cell adenoma), and cancer of the bone (osteosarcoma) and nasal cavity (carcinoma) in males and benign mammary-gland tumors (fibroma or fibroadenoma) in females (Soffritti et al. 2002). Increased incidences of tumors observed at other sites occurred only at one of the lower doses tested."

5. MECHANISTIC CONSIDERATIONS AND OTHER RELEVANT DATA

5.1 Pharmacokinetics and Metabolism

5.1.1 Overview

The pharmacokinetics and metabolism of vinyl acetate have been studied in humans and animals *in vivo* and *in vitro*, and in cell-free systems. OEHHA reviewed studies that provide relevant information on (i) pharmacokinetics, (ii) metabolism, including reactive metabolites and DNA adduct formation, and (iii) human polymorphisms of key enzymes. Since humans and animals share many of the reported metabolic pathways and metabolites, data from animal studies are included when human data are unavailable or incomplete, when data from animal studies are useful to complement human data, and when route, species, and gender differences are observed.

Human studies included one *in vivo* study via inhalation, and several *in vitro* studies. Animal studies included *in vivo* studies conducted in multiple strains of rats and mice (including knock-out mice), and in guinea pigs, as well as several *in vitro* studies. Studies in cell free systems were also identified. Exposure routes used in the *in vivo* studies included inhalation, oral gavage, and intraperitoneal (*i.p*.) injections. An overview of key findings from these studies is provided here.

Vinyl acetate is quickly absorbed and distributed throughout the body. It is largely excreted within 24 hours in expired air, urine and feces (Cresswell et al. 1979; Hinderliter et al. 2005; Plowchalk et al. 1997; Strong et al. 1980). Upon absorption, carboxylesterases (CES) metabolize vinyl acetate to acetic acid and vinyl alcohol, the latter of which quickly rearranges to acetaldehyde (Bogdanffy and Taylor 1993; Bogdanffy and Valentine 2003). Acetaldehyde is a known genotoxic carcinogen (IARC 1999; OEHHA 1988). Acetaldehyde is further oxidized to acetic acid via aldehyde dehydrogenases (primarily aldehyde dehydrogenase 2 (ALDH2)) and is introduced into the tricarboxylic acid (Krebs) cycle where it is further metabolized (Bogdanffy and Valentine 2003; ECHA 2008). The oxidation of acetaldehyde and ionization of acetic acid at physiological pH release protons, which contribute to some cellular acidification (Bogdanffy and Valentine 2003). DNA adducts and DNA-protein crosslinks (DPXL) have been observed with vinyl acetate or acetaldehyde treatment in rodent *in vivo* and *in vitro* studies (Hsiao et al. 2022; Kuykendall et al. 1993; Liu et al. 2021; Oyama et al. 2010).

In other metabolic reactions, vinyl acetate can be conjugated with reduced glutathione (GSH) (Boyland and Chasseaud 1967, 1970; Holub and Tarkowski 1982). Downstream of vinyl acetate, acetaldehyde can be metabolized by cytochrome P450 (CYP)

enzymes, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), xanthine oxidase, or aldehyde oxidase, with the latter two enzymes generating reactive oxygen species (ROS) and xanthine oxidase also producing alkyl radicals (Albano et al. 1994; Fridovich 1966; Kunitoh et al. 1996; Kunitoh et al. 1997; Nakao et al. 2000; Puntarulo and Cederbaum 1989; Shaw and Jayatilleke 1990a, b).

OEHHA also reviewed studies on various factors, including genetic polymorphisms, affecting the activity of CES and ALDHs involved in the metabolism of vinyl acetate. For example, ALDH2 polymorphisms can result in a decreased or complete lack of the ability to metabolize acetaldehyde, leading to build-up of this genotoxic vinyl acetate metabolite (Ginsberg et al. 2002). These studies are discussed at the end of this chapter.

5.1.2 Absorption

Few studies included data related to the absorption of vinyl acetate. Uptake of vinyl acetate following inhalation appears to be rapid in humans (Bogdanffy et al. 1998; Hinderliter et al. 2005) and rats (Simon et al. 1985a). In rats, saturation of vinyl acetate uptake by inhalation at higher concentrations has been observed (> 650 ppm in Simon et al. (1985a); or around 1500 to 2000 ppm in Plowchalk et al. (1997)).

Human volunteers were exposed to low levels (1, 5, and 10 ppm) of $^{13}C_1$,$^{13}C_2$ vinyl acetate by inhalation and an inserted nasopharyngeal probe sampled both the concentration of $^{13}C_1$,$^{13}C_2$ vinyl acetate and its metabolite, $^{13}C_1$,$^{13}C_2$ acetaldehyde in the nasal cavity during short periods (2- to 5-minute intervals) of resting and light exercise (Hinderliter et al. 2005). The study measured the uptake of inhaled vinyl acetate in the nasal cavity and the concentration of acetaldehyde released into the nasal cavity. Measured concentrations of ^{13}C-labeled vinyl acetate and acetaldehyde indicated that vinyl acetate was rapidly absorbed by nasopharyngeal tissues and metabolized. In an *in vitro* gas uptake study using whole sections of human nasal tissues obtained within two hours of death, rapid uptake of vinyl acetate and metabolism to acetaldehyde were observed within minutes (Bogdanffy et al. 1998).

In male Wistar rats, gas uptake of vinyl acetate (200–2000 ppm) also occurred rapidly with linear increases up to 650 ppm (Simon et al. 1985a). Concentration-dependent uptake in the upper respiratory tract was also observed in male CrlCD:BR rats, where removal of vinyl acetate from the air and disposition into nasal tissues was highly efficient (> 93%) at lower vinyl acetate concentrations (below 76 ppm), decreased to about 40% as vinyl acetate concentrations increased to 550 ppm, and remained at the same level up to 2000 ppm vinyl acetate (Plowchalk et al. 1997).

In incubation studies with human whole blood or red blood cells, vinyl acetate undergoes rapid enzymatic hydrolysis. The half-life of vinyl acetate with whole blood

occurs within approximately 3–4 minutes, and with red blood cells within approximately 5.5 minutes. Incubations with human plasma yielded little degradation, with a half-life of 62 minutes and a V_{max} (maximum velocity of an enzymatic reaction) of 0.69 µmol/min per mg protein (Fedtke and Wiegand 1990; Simon et al. 1985a; Strong et al. 1980).

The half-life of vinyl acetate was also measured in incubation studies with various tissues of rats and mice. In rat blood (SD and Wistar rats), the half-life was short, ranging from approximately 1 minute to just over 2 minutes in whole blood, about 1 minute in plasma, and 5.6 minutes in red blood cells (Cresswell et al. 1979; Fedtke and Wiegand 1990). The V_{max} in rat plasma was 0.56 µmol/min per mg protein, compared to the values reported for rat liver and lung microsomes of 23 and 6.2 µmol/min per mg protein, respectively (Simon et al. 1985a). The half-life of vinyl acetate in mouse plasma (CD1 strain Albino SPF) was 36 seconds, and just under 2 minutes in whole blood. In mouse liver homogenate, vinyl acetate had a half-life of 1 minute (Cresswell et al. 1979).

The dermal absorption of vinyl acetate has not been directly measured. However, two studies in rabbits reported mortality following dermal application of vinyl acetate, indicating that absorption via skin occurs. In one study in rabbits, mortality was observed following dermal exposure to 2.5 ml/kg vinyl acetate (Smyth and Carpenter 1948). A second dermal application study, reviewed by ECHA (2008), also reported lethality to rabbits following dermal exposure to vinyl acetate.[12]

5.1.3 Distribution

Tissue distribution of vinyl acetate was determined in male and female SD rats following inhalation or oral exposure with (vinyl-1-2-^{14}C) vinyl acetate. Inhalation doses were 1000 ppm (Cresswell et al. 1979) and 750 ppm (vinyl-1-2-^{14}C) vinyl acetate (Strong et al. 1980), both for 6 hours (hr). Sampling occurred at 0, 1, 6, and 72 hr post dosing. Oral exposures were by gavage, as a single administration of 1 ml of 5000 ppm (vinyl-1-2-^{14}C) vinyl acetate (Cresswell et al. 1979) and as six administrations, 1 hr apart, of 1 ml of 10,000 ppm (vinyl-1-2-^{14}C) vinyl acetate (Strong et al. 1980). Sampling occurred at 1, 6, and 72 hr post the last dosing. The study by Cresswell et al. (1979) reported radioactivity as qualitative data based on whole animal sections; Strong et al. (1980) reported radioactivity quantitatively for each organ examined.

In these studies, radioactivity was distributed throughout the body, with highest levels of radioactivity found in the Harderian gland, salivary gland, larynx, stomach, gastrointestinal (GI) tract, colon, kidney, liver, lung, brain, and ovaries. The lowest levels

[12] OEHHA could not locate the following original study and relied on ECHA's review: Mellon Institute (1969). Range finding toxicity studies. Report 32-99, Sponsor: Union Carbide.

of radioactivity were reported for fat, skeletal muscle, heart, and blood. High levels of radioactivity were also reported for the nasoturbinates and ethmoturbinates following inhalation but not oral exposure (Cresswell et al. 1979). After 72 hours radioactivity was largely eliminated from most tissues in all studies.

Strong et al. (1980) also conducted whole body autoradiography of rats and mice following a single oral dose of ^{14}C-acetaldehyde in male and female SD rats and of ^{14}C-vinyl acetate in male and female albino SPF mice (CD-1). In rats dosed with ^{14}C-acetaldehyde, one hour post exposure whole body sections showed high levels of radioactivity in the Harderian, salivary, and lingual glands, the GI mucosa, liver, thymus, and lymph nodes. Low levels were observed in blood, muscle, and fat. No differences between sexes were reported. The results of ^{14}C-vinyl acetate exposure in mice were very similar to the findings of ^{14}C-acetaldehyde in rats, with the greatest radioactivity found in the Harderian, salivary, and lingual glands, the GI mucosa, liver and brown fat. Lower levels of radioactivity were present in blood, muscle, fat and testes, with no differences between sexes reported.

5.1.4 Elimination

Excretion of (vinyl-1-2-^{14}C) vinyl acetate was measured in male and female SD rats following dosing via inhalation or gavage (Cresswell et al. 1979; Strong et al. 1980). Regardless of route, the majority of radioactivity was excreted into expired air. Urinary and fecal excretion were minor. There was no difference in the pattern of elimination between male and female rats.

Elimination of vinyl acetate was studied with inhalation exposures to 750 ppm (Strong et al. 1980) or 1000 ppm (Cresswell et al. 1979) of (vinyl-1-2-^{14}C) vinyl acetate in male and female SD rats (Table 27). Vinyl acetate was primarily excreted as CO_2 in the expired air; urine contained one major and several minor radioactive fractions, with the major fraction having a retention time similar to urea; the remaining minor fractions were unidentified. In other studies, acetaldehyde was reported in expired air in humans (Hinderliter et al. 2005) and rats (Plowchalk et al. 1997; Simon et al. 1985a) after vinyl acetate exposure. Expired acetaldehyde increased with increasing concentrations of vinyl acetate, with a maximum of 277 ppm acetaldehyde measured in expired air following exposure to approximately 1000 ppm vinyl acetate (Plowchalk et al. 1997).

Elimination following oral exposure was similar to inhalation exposure, with the majority of radioactivity excreted as CO_2 via expired air within 96 hours (Cresswell et al. 1979; Strong et al. 1980) (see Table 27).

Table 27. (Vinyl-1-2-^{14}C) vinyl acetate excretion in rats under different exposure conditions (Cresswell et al. 1979; Strong et al. 1980)

Exposure route	Inhalation		Oral gavage	
Exposure conditions	1000 ppm for 6 hr	750 ppm for 6 hr	1 ml of 5000 ppm	1 ml of 10000 ppm every hr, for 6 hr
% radioactivity in exhaled air	70.3%	74.6%	86.3%	61.2%
% radioactivity in urine	7.1%	4.8%	3.4%	1.8%
% radioactivity in feces	3.9%	3.6%	1.1%	1.4%
Sum	81.3%	83.0%	90.8%	64.4% [a]
Reference	Cresswell et al. (1979)	Strong et al. (1980)	Cresswell et al. (1979)	Strong et al. (1980)

Radioactivity was measured at 96 hours after exposure.

[a] About 30% of radioactivity could be lost via exhaled CO_2 during the hourly removal of the animals from the test cage, per authors.

5.1.5 Metabolism

As briefly outlined above, the metabolism of vinyl acetate mainly involves two key enzymes: CES and ALDH2. In an initial reaction, vinyl acetate is hydrolyzed by CES to form acetic acid and vinyl alcohol, the latter of which rearranges to acetaldehyde. Acetaldehyde is primarily metabolized by ALDH2 to acetic acid, which in turn reacts with Coenzyme A (CoA) via acetyl-CoA synthase and is introduced into the tricarboxylic acid (Krebs) cycle for further metabolism (Figure 2) (Bogdanffy and Valentine 2003). Acetaldehyde is a known carcinogen that is genotoxic *in vitro* and *in vivo* in multiple systems and which induces tumors in rodents, including nasal tumors in rats (Albertini 2013; IARC 1999). The genotoxicity of acetaldehyde is discussed in more detail under KC2.

Localized metabolism studies of vinyl acetate, plus histocytochemical observations, indicate that both CES and ALDH2 are present in human nasal tissues as well as in rat and mouse respiratory and oral cavity tissues. CES and ALDH from rats have two- and three-times greater enzyme activity, respectively, compared to their human counterparts (Bogdanffy et al. 1986, 1987; Bogdanffy et al. 1998; Casanova-Schmitz et al. 1984;

Hinderliter et al. 2005; Morris et al. 2002; Robinson et al. 2002). In rats, differences in enzyme distribution and activity in nasal tissues indicate that olfactory epithelial tissues have high CES but low ALDH2 activity, suggesting that acetaldehyde removal from these tissues may be impeded (Bogdanffy et al. 1986, 1987; Bogdanffy and Taylor 1993). In rat respiratory and olfactory turbinates, metabolism of 50 mM vinyl acetate (measured as acetaldehyde) increased in a time-dependent manner and plateaued in the respiratory epithelium at 16 mM acetaldehyde (Kuykendall et al. 1993).

The metabolism of vinyl acetate by CES can lead to slight intracellular acidification via the release of protons from the NAD^+-dependent ALDH2 oxidation and disassociation of protons from acetic acid at physiological pH. This has been observed *in vitro* in isolated rat hepatocytes (Bogdanffy 2002), rat respiratory and olfactory nasal cells (Lantz et al. 2003), and mouse buccal epithelium (Nakamoto et al. 2005). The measured intracellular pH changes were relatively small, resulting in a change of 0.3 pH units when cells were incubated with 1 mM vinyl acetate (Lantz et al. 2003; Nakamoto et al. 2005). Ten µM vinyl acetate was the minimum concentration to produce a statistically significant change in intracellular pH (0.03 pH units) in rat hepatocytes (Bogdanffy 2002). The observed decrease in pH was dose-dependent up to 200 and 250 µM vinyl acetate in hepatocytes and rat nasal epithelial cells, respectively (Bogdanffy 2002; Lantz et al. 2003). No cytotoxicity was observed in hepatocytes incubated with vinyl acetate concentrations of up to 1000 µM (1 mM) (Bogdanffy 2002). Intracellular acidification was reduced or reversed when vinyl acetate was removed from the incubation medium (Nakamoto et al. 2005) or when the CES inhibitor *bis*(*p*-nitrophenyl)phosphate (BNPP) was added. Some authors suggest that intracellular acidification may be a sentinel event that precedes cytotoxicity and cellular proliferation (Bogdanffy and Valentine 2003; Nakamoto et al. 2005).

The balance between metabolic activation of vinyl acetate via CES and clearance of the metabolite acetaldehyde by ALDH2 largely determines the overall level of acetaldehyde in a cell or tissue, with ALDH2 playing a critical role as the detoxifying agent. Rapid generation of acetaldehyde, coupled with slow clearance, may lead to increased levels of acetaldehyde following vinyl acetate exposure. Because acetaldehyde is also produced endogenously, exogenous sources of acetaldehyde may disturb the intra-cellular homeostasis of acetaldehyde, which is maintained by a fully functioning ALDH2 (Albertini 2013).

Below we describe in more detail information relevant to the activities of CES and ALDH2 in the context of exposure to vinyl acetate and the resulting formation of acetaldehyde, including distribution in the body, enzyme characteristics, polymorphisms, and additional pathways of acetaldehyde metabolism leading to the formation of radicals, reactive oxygen species (ROS), DNA and DNA-protein crosslinks and DNA adducts.

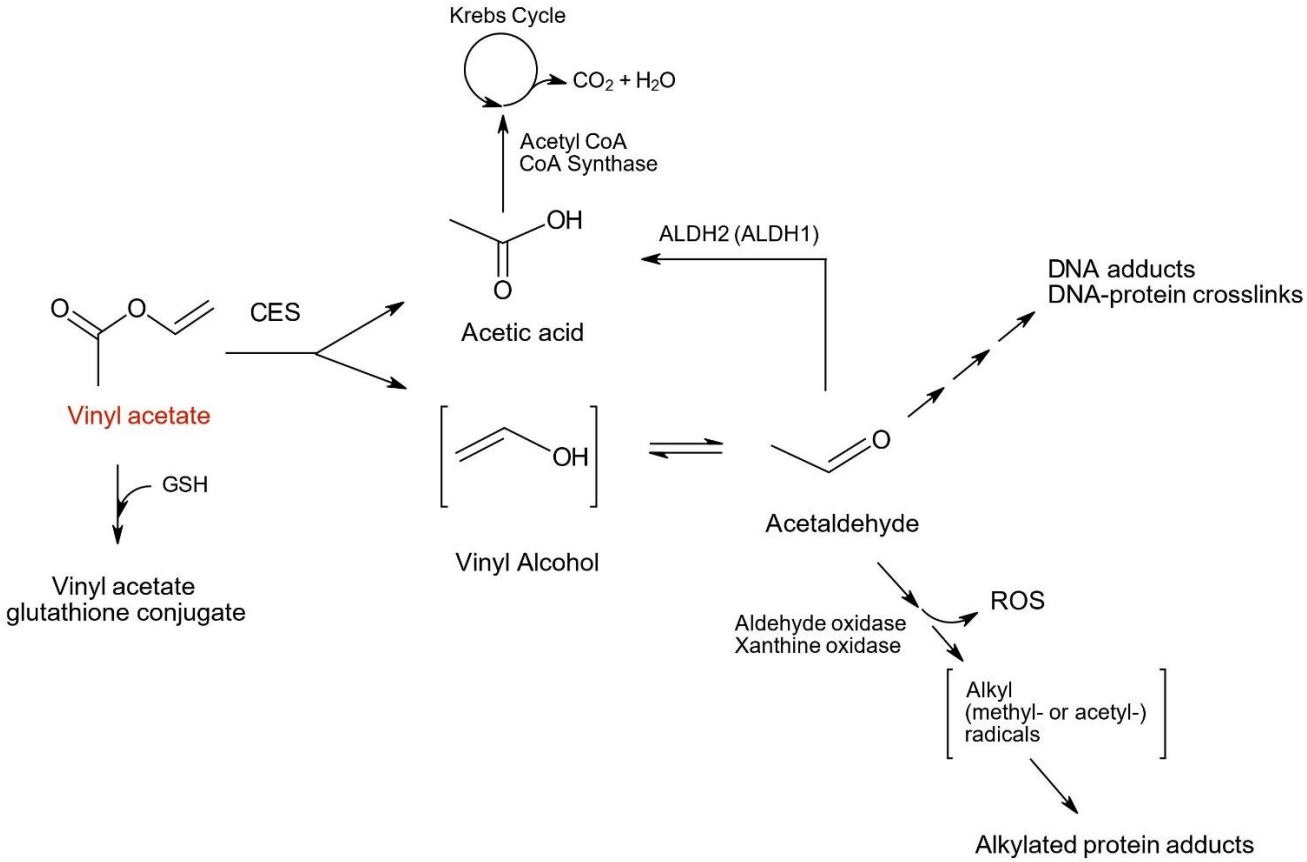

Figure 2. Major metabolic pathways of vinyl acetate.
Some metabolic reactions of acetaldehyde, such as those carried out by CYP enzymes and GAPDH, are not shown in the figure. See text for details.

5.1.5.1 Vinyl acetate metabolism via carboxylesterases (CES)

Hydrolysis of vinyl acetate via CES is the first step in its metabolism, resulting in the formation of acetic acid and vinyl alcohol, the latter of which quickly rearranges to acetaldehyde. The hydrolysis reaction can be inhibited when animals, cells or tissues are treated with the CES inhibitor BNPP. For example, about a 55% reduction of vinyl acetate metabolism was observed when rats were pretreated with BNPP (Bogdanffy et al. 1999).

CES are found in the lumen of the endoplasmic reticulum and exist in six isoforms, with CES1 and CES2 involved in metabolism of xenobiotics, including vinyl acetate. CES are widely distributed in the human body, with the highest concentrations in the liver and GI tract, and are present at lower levels in the lung, nasal cavity, skin, plasma, and placenta, with little activity detected in human blood (Di Consiglio et al. 2021; Di 2019; Laizure and Parker 2020; Wang et al. 2018; Zhang et al. 2002). By contrast, high CES

activity levels have been measured in rodent blood (Wang et al. 2018). CES activity levels have been measured in nasal tissues from rats and mice, with an estimated V_{max} ranging from 22 to 46 µmol/min/mg protein and a K_m (Michaelis constant) ranging from 0.3 to 1.07 mM (Bogdanffy and Taylor 1993).

CES expression is developmentally regulated and activity increases in the first few weeks after birth, but remains lower in children compared to adults. Other factors that may affect CES expression and/or activity include genetic polymorphisms, hormones, disease state, nutritional status, drugs, and exposures to environmental chemicals. Genetic polymorphisms of CES1 and CES2 can impact enzyme activity and lead to inter-individual differences in xenobiotic metabolism (Di Consiglio et al. 2021; Di 2019). Several polymorphisms of *CES1* and *CES2* have been identified in human populations (Cha et al. 2014; Chen et al. 2018; Marsh et al. 2004). Many of these polymorphisms are synonymous mutations that do not alter the protein sequence or conformation; however, among those that do alter the protein sequence or conformation, some result in decreased enzyme activity (e.g., G143E, rs7167871), while others do not. One study reported that the allele frequency of *CES1* rs7167871, a polymorphism that results in slower conversion of vinyl acetate to acetaldehyde, was 3.7% in Caucasian participants, 4.3% in African participants, 2% in Hispanic participants, and 0% in Asian participants (Zhu et al. 2008). However, no specific information on the impact of CES polymorphisms on enzymatic activity using vinyl acetate as the substrate was identified in OEHHA's literature search.

Vinyl acetate induces cytotoxicity in rat nasal turbinate explants (Kuykendall et al. 1993). This cytotoxicity requires CES-mediated metabolic activation, as shown by reduced cytotoxicity when rats were treated with the CES inhibitor BNPP prior to nasal turbinate removal and incubation with vinyl acetate. Cytotoxicity in the explants was measured as the time-dependent release of intracellular acid phosphatase into the incubation medium and was attributed to the action of acetic acid, rather than acetaldehyde, based on observations that addition of the aldehyde scavenger semicarbazide to the incubation did not protect against the vinyl acetate-induced cytotoxicity.

Formation of DPXLs has also been observed in isolated rat olfactory and respiratory nasal cells following exposure to vinyl acetate (5–75 mM) or acetaldehyde (10–150 mM) for one to two hours (Kuykendall et al. 1993). Treatment with the CES inhibitor BNPP inhibited the formation of vinyl acetate induced DPXLs in a dose-dependent manner (Kuykendall et al. 1993). Increases in vinyl acetate induced DPXLs were time- and dose-dependent, with higher increases observed in olfactory compared to respiratory epithelial cells (Kuykendall et al. 1993). These findings are consistent with studies reporting that carboxylesterase activity was twice as high in rat microsomes prepared from olfactory mucosa as compared to respiratory mucosa (Bogdanffy et al. 1999). In

two other studies, vinyl acetate treatment resulted in the formation of DNA adducts in rat nasal respiratory and olfactory epithelia *in vivo*; the adducts were thought to be caused by vinyl acetate-derived acetaldehyde (Hsiao et al. 2022; Liu et al. 2021). Both adduct formation and DNA lesions are also described under KC1 and KC2.

5.1.5.2 Vinyl acetate metabolism via glutathione conjugation

Vinyl acetate can be conjugated with reduced glutathione (GSH), as shown in multiple rodent species *in vivo* (Boyland and Chasseaud 1970; Holub and Tarkowski 1982) and in an *in vitro* study (Boyland and Chasseaud 1967). A 23% decrease in liver GSH was observed in female rats 30 minutes after an *i.p.* injection with vinyl acetate. At two hours post injection, GSH levels had rebounded, increasing to about 150% of control levels (Boyland and Chasseaud 1970).

Holub and Tarkowski (1982) also reported GSH conjugation in guinea pigs, mice, and rats following a single *i.p.* injection of vinyl acetate (guinea pigs (500 mg/kg), mice (300 mg/kg), rats (300 and 450 mg/kg)). A rapid and significant decrease (50%) of hepatic GSH was observed in guinea pigs within 30 minutes. Mice and rats had slower and smaller decreases in GSH, with a significant 23% reduction occurring in mice over a four-hour period and a low but statistically significant ten percent reduction occurring in rats within four hours at the high dose only. The same study also found that chronic inhalation exposure (5 hours/day for 6 months) of rats to 10, 100, or 500 mg/m^3 vinyl acetate resulted in an approximate 20 percent reduction of hepatic GSH levels.

5.1.5.3 Acetaldehyde metabolism via aldehyde dehydrogenases (ALDH)

ALDH can oxidize acetaldehyde to acetic acid. There are about 19 ALDH members in the *ALDH* gene family, with ALDH2 being the most efficient enzyme to metabolize acetaldehyde based on its high affinity, i.e., low K_m (as low as 0.2 µM), for acetaldehyde (Ginsberg et al. 2002; Rashkovetsky et al. 1994; Wang et al. 2020), followed by ALDH1 (Singh et al. 2015; Stagos et al. 2010). ALDH2 is widely distributed in fetal and adult tissues, with the highest levels in adults reported in the liver, followed by lung, kidney, and skeletal and heart muscles (Deitrich et al. 2007; Stewart et al. 1996). Similarly, fetal mRNA expression of ALDH2 was highest in the liver, followed by heart, lung, kidney, and brain tissues (Stewart et al. 1996). On a subcellular level, ALDH2 is localized in the mitochondrial matrix (Deitrich et al. 2007).

The metabolic efficiency of ALDH2 is highly impacted by genetic polymorphisms, which can lead to a partial or complete loss of function and thus can increase the levels of the toxic and carcinogenic metabolite acetaldehyde. Several ALDH2 allelic forms have been examined, with most studies focusing on rs671, a point mutation that results in an amino acid change from glutamic acid to lysine (Glu504Lys). This allele is commonly denoted as ALDH2*2. ALDH2*2 impairs the enzyme by interfering with its ability to form a tetramer and thus confers a dominant negative phenotype (Xiao et al. 1996). Allelic

forms include the homozygous wildtype ALDH2*1/*1 with full activity, the heterozygous ALDH2*1/*2 with intermediate enzyme activity, and the homozygous variant ALDH2*2/*2 with no enzyme activity (Ginsberg et al. 2002; Vasiliou and Pappa 2000). The non-functional allele *2 is common in East Asian populations, with up to 40% being heterozygous and another 5–10% being homozygous (Ginsberg et al. 2002; Li et al. 2009).

The reduced or non-functioning ALDH2 variants can result in significant build-up of acetaldehyde. A study with healthy male volunteers from Japan showed that acetaldehyde levels in blood, following ingestion of ethanol (0.4 g/kg-bw over 10 minutes), increased from 4.1 µM in subjects with the *ALDH2*1/*1* genotype (N = 33) to 23.4 µM in heterozygous *ALDH2*1/*2* carriers (N = 29) and to 79.3 µM in carriers with the homozygous *ALDH2*2/*2* genotype (N = 6) (Mizoi et al. 1994).

In addition to certain ALDH2 polymorphisms, repression and/or lack of ALDH2 activity by other factors such as taking pharmaceutical ALDH2 inhibitors (e.g., disulfiram) also leads to increased levels of acetaldehyde, which in turn can result in DNA damage and the formation of DNA adducts. Increased levels of acetaldehyde were observed *in vitro* in human lung cancer cells (A549) with repressed expression of ALDH2 (A549-shALDH2 cells) (Li et al. 2019). And in additional experiments, increased acetaldehyde-induced DNA damage was measured in A549-GFP cells (A549 cells with normal ALDH2 expression) compared to A549-ALDH2 cells which overexpressed ALDH2 (Li et al. 2019). Li et al. (2019) also reported accumulation of acetaldehyde and increased DNA damage (measured as γH2AX) in lung tissues from Aldh2-knockout mice *in vivo*. In another study male C57BL/6 wildtype and knockout mice ($Aldh2^{-/-}$) were exposed to 125 and 500 ppm of acetaldehyde for 14 days via inhalation. In the knockout mice lacking the ALDH2 enzyme acetaldehyde levels in the blood were increased five-fold in the 500 ppm group compared to controls (Oyama et al. 2010). Oyama et al. (2010) also observed significant increases of N^2-ethylidene-dG (measured in its reduced form as N^2-ethyl-dG) adducts in the knockout mice in the nasal epithelium, lung, and dorsal skin compared to wildtype mice. No differences in adduct levels were observed in the livers of knockout compared to wildtype mice.

ALDH2 polymorphisms and risk of cancer

While no studies were identified regarding the effect of ALDH2 polymorphisms on the potential cancer risk of vinyl acetate, many studies investigated the associations between alcohol consumption, ALDH2 polymorphisms and risks of various cancer types, and the potential gene-environment interaction between ALDH2 polymorphisms and alcohol consumption. Carrying the ALDH2*2 allele, especially the homozygous genotype, has been associated with an increased risk of multiple cancers, including oropharyngolaryngeal, esophageal, gastric, colon, lung, head and neck cancers (Gao et

al. 2008; Kang et al. 2021; Marchitti et al. 2008; Yang et al. 2009; Yokoyama et al. 1998; Yokoyama and Omori 2003). In general, ALDH2 polymorphisms are associated with increases in cancer risk, shorter time to tumor recurrence, and higher mortality compared to their ALDH2*1/*1 counterparts when taking into account similar levels of alcohol consumption (Zhang and Fu 2021). On the other hand, there are studies that found no increased risk or decreased risk of cancer with having the ALDH2*2 allele (Matsuo et al. 2006; Yin et al. 2007; Yin et al. 2011) or no gene-environment interaction between alcohol consumption and this polymorphism (Ugai et al. 2019; Yang et al. 2017). Interpretation of these studies is challenging as the observed cancer risk can depend on multiple factors, including additional polymorphic enzymes (e.g., alcohol dehydrogenase for studies with alcohol consumption), additional polymorphisms, tissue specific effects, and lifestyle factors. There is also the issue of minimal exposure contrast; several studies have shown that carriers of the ALDH2*2 polymorphism are less likely to become alcoholics and drink less than their ALDH2*1/*1 counterparts, and thus may have lower exposure when considering cancer risk from ethanol and acetaldehyde.

5.1.5.4 Other metabolic reactions of acetaldehyde

Vinyl acetate's metabolite acetaldehyde can undergo other enzymatic reactions in addition to those discussed above. It can be metabolized by GAPDH, CYP enzymes, xanthine oxidase, and aldehyde oxidase. Oxidation via xanthine oxidase and aldehyde oxidase produces ROS *in vivo* and *in vitro* and in cell free systems; production of alkyl radicals has also been reported via xanthine oxidase catalyzed oxidation (Albano et al. 1994; Mira et al. 1995; Nakao et al. 2000; Puntarulo and Cederbaum 1989; Ryzlak and Pietruszko 1989).

Phosphorylation via GAPDH

Mitochondrial GAPDH isolated from human brain can phosphorylate acetaldehyde to form acetyl phosphate (Ryzlak and Pietruszko 1989). However, due to the very high Km for acetaldehyde (300–2000 µM), this reaction is unlikely to play a role in acetaldehyde metabolism under physiological conditions.

Oxidation via CYP enzymes

Acetaldehyde can be metabolized to acetic acid by CYP2E1, which has been shown *in vitro* using human recombinant CYP2E1 and rat liver microsomes (Bell-Parikh and Guengerich 1999; Kunitoh et al. 1996; Kunitoh et al. 1997; Terelius et al. 1991). However, CYP2E1 may not be a key metabolizing enzyme based on an inhalation study in rats conducted by Bogdanffy et al. (1999), where pre-treatment with diallyl sulfide, a CYP2E1 inhibitor, showed no significant effect on vinyl acetate metabolism (assessed

by measuring levels of expired acetaldehyde, and by calculating the efficiency of vinyl acetate extraction from the air by the rat nasal cavity).

Oxidation via xanthine oxidase

Oxidation of acetaldehyde via xanthine oxidase leads to the formation of alkyl radicals, reactive oxygen species (e.g., superoxide anion, hydrogen peroxide, and hydroxyl radicals), and alkylation of proteins. Carbon-centered radicals (methylcarbonyl radicals) were observed in cell-free systems when acetaldehyde was incubated with xanthine oxidase. The formation of carbon-centered radicals was dependent on the concentration of added acetaldehyde, whereas the addition of a hydroxyl radical scavenger (4-pyridyl-1-oxide-N-*t*-butyl nitrone), superoxide dismutase (SOD), or catalase inhibited methylcarbonyl radical formation and the formation of alkylated protein adducts (Albano et al. 1994). The generation of hydroxyl radical from acetaldehyde via xanthine oxidase was also assessed via chemiluminescence. Chemiluminescence by acetaldehyde following oxidation with xanthine oxidase was inhibited by the addition of SOD, catalase, and hydroxyl radical scavengers, suggesting hydroxyl radicals are produced (Puntarulo and Cederbaum 1989).

Following intragastric administration of acetaldehyde (1 g/kg), methyl radicals were identified in cannulated bile samples of male SD rats, along with strong evidence indicative of acetyl radical formation (Nakao et al. 2000). Similarly, production of acetyl and methyl radicals was observed when beef heart submitochondrial particles (formed from the inner mitochondrial membrane) were incubated with acetaldehyde (Nakao et al. 2000). These authors also showed in a cell-free system that production of acetyl and methyl radicals via xanthine oxidase-catalyzed oxidation of acetaldehyde was significantly reduced in the presence of the xanthine oxidase inhibitor allopurinol (Nakao et al. 2000).

Oxidation via aldehyde oxidase

The oxidation of acetaldehyde via aldehyde oxidase also generates ROS, including superoxide anion radical, hydrogen peroxide, and hydroxyl radical (Mira et al. 1995; Shaw and Jayatilleke 1990a, b). Using a cell-free system, the formation of superoxide during the oxidation of acetaldehyde with aldehyde oxidase from rat liver was observed (Mira et al. 1995).

Incubations of rat hepatocytes with physiological concentrations of acetaldehyde (up to 100 µM) initiated lipid peroxidation, measured as the production of ethane and pentane, in a dose-dependent manner (Shaw and Jayatilleke 1990a). Through use of specific inhibitors of aldehyde oxidase (menadione) and xanthine oxidase (allopurinol), and the iron chelator desferrioxamine, the authors demonstrated the key role of aldehyde oxidase. Specifically, aldehyde oxidase-mediated oxidation of acetaldehyde was shown to be primarily responsible for the generation of ROS (e.g., the iron-catalyzed formation

of hydroxyl radicals from superoxide anion and hydrogen peroxide) and subsequent lipid peroxidation.

5.1.5.5 Summary of metabolism

In summary, vinyl acetate is metabolized to acetic acid and acetaldehyde via CES and ALDH2 enzymes. Acetic acid undergoes further metabolism via the tricarboxylic acid cycle. Acetaldehyde can react with DNA and proteins to form DNA adducts and DPXLs. Acetaldehyde can also undergo further metabolism by other enzymes, such as xanthine oxidase and aldehyde oxidase, which can result in formation of ROS and alkyl radicals. ALDH2 plays a key role in detoxifying acetaldehyde. Genetic polymorphisms of ALDH2 can result in a partial or complete loss of function of this enzyme, resulting in increased levels of acetaldehyde which in turn increases the formation of ROS, carbon-centered radicals, DNA and/or protein adducts, and DPXLs.

5.2 Key Characteristics of Carcinogens

A comprehensive review of the more than 100 agents known to cause cancer in humans identified 10 key characteristics (KCs) of carcinogens (Samet et al. 2020; Smith et al. 2016) (Table 28). As the name implies, KCs are characteristics of agents that cause cancer, in contrast to the hallmarks of cancer (Hanahan and Weinberg 2000, 2011), which are properties of cancer cells and neoplasms, and also in contrast to modes of action, which are sequences of key events that transform normal cells into malignant tumors. Mode of action analysis depends on prior knowledge sufficient to hypothesize how an agent might cause cancer, knowledge that too often is incomplete. The KCs can encompass many types of mechanistic endpoints and are not constrained to previously formulated hypotheses, allowing a broader consideration of multiple mechanistic pathways and hypotheses.

Table 28. Key characteristics of carcinogens

Key characteristic	Example of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (*e.g.,* epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, UDS), intercalation, gene mutations, cytogenetic changes (*e.g.,* CAs, MN)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (*e.g.,* topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (*e.g.,* DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor inactivation/activation (*e.g.,* ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Source: Smith et al. (2016) and Samet et al. (2020)
AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (*e.g.*, oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

OEHHA used the KCs approach to systematically identify, organize, and summarize information on mechanisms of carcinogenesis for vinyl acetate. Data for 3 of the 10 KCs, namely KCs 1, 2, and 10, were identified and summarized in the following sections. Overall, mechanistic data support the observations that vinyl acetate can be metabolically activated to an electrophilic chemical (acetaldehyde) and form DNA

adducts, causes genotoxicity including clastogenicity and DNA damage, and can induce cell proliferation and pre-neoplastic lesions such as hyperplasia and dysplasia.

5.2.1 Is electrophilic or can be metabolically activated (KC1)

Electrophiles are reactive, electron-seeking molecules capable of binding to electron-rich cellular macromolecules including DNA, RNA, lipids, and proteins, thereby forming covalent adducts. The measurement of covalent adducts on DNA and proteins is the most common method of assessing electrophilic activity (Smith et al. 2020).

Vinyl acetate is metabolized by carboxylesterases (CES) to acetic acid and vinyl alcohol, the latter of which quickly rearranges to form the reactive metabolite, acetaldehyde (see Section 5.1.5, Metabolism, and Figure 2). Although few studies have explicitly focused on vinyl acetate exposures and the associated DNA adducts, much is known about acetaldehyde-derived DNA adducts from studies of direct exposure to acetaldehyde. Below is a summary of available studies of vinyl acetate and DNA adduct formation (resulting from its metabolite acetaldehyde), followed by a brief summary of the data from studies of direct exposure to acetaldehyde.

Rat studies of exposure to vinyl acetate: DNA adduct formation

- To differentiate between DNA adducts caused by vinyl acetate treatment and adducts caused by other (e.g., endogenous) sources of acetaldehyde, rats were treated with [$^{13}C_2$]-vinyl acetate (50, 200, or 400 ppm) via inhalation for 6 hr (Liu et al. 2021). The vinyl acetate-derived DNA adduct [$^{13}C_2$]-N^2-ethyl-2'-deoxyguanosine (N^2-Ethyl-dG) was detected in nasal respiratory and olfactory epithelia in a dose-dependent manner. [$^{13}C_4$]-1,N^2-propano-dG (N^2-propano-dG) adducts were also detected in the respiratory epithelia of rats exposed to 400 ppm [$^{13}C_2$]-vinyl acetate, although these adducts were present at lower levels in these animals than [$^{13}C_2$]-N^2-Ethyl-dG. Furthermore, low amounts of [$^{13}C_2$]-N^2-Ethyl-dG adducts in the peripheral blood mononuclear cells were detected in all vinyl acetate treated groups, indicating systemic effects of vinyl acetate exposure, beyond the nasal epithelia.
- In another study using lower vinyl acetate exposures over multiple days, [$^{13}C_2$]-N^2-Ethyl-dG adducts were detected in the nasal respiratory and olfactory epithelia of rats treated with [$^{13}C_2$]-vinyl acetate (10 or 50 ppm) via inhalation for 6 hr/day for 14 days (Hsiao et al. 2022). Low amounts of [$^{13}C_2$]-N^2-Ethyl-dG adducts were also detected in one of three pooled samples of peripheral blood mononuclear cells of rats exposed to 50 ppm [$^{13}C_2$]-vinyl acetate. No vinyl acetate-derived adducts were detected in the liver, brain, or bone marrow of exposed rats.

- A targeted search for two known DNA adducts of vinyl halides and vinyl carbamate (i.e., 7-(2-oxoethyl)guanosine and N2, 3-ethenoguanosine) in livers of rats exposed to ^{14}C-vinyl acetate was conducted, 4 hr after either a 90-min inhalation exposure or a single oral gavage dose (Simon et al. 1985b). Neither of these vinyl halides or vinyl carbamate-associated adducts was detected in the livers of rats exposed to ^{14}C-vinyl acetate.

Studies of direct exposure to acetaldehyde: DNA adduct formation

Numerous studies have shown that acetaldehyde can bind to DNA, including studies conducted in cell-free systems, non-human and human cells, and rodents (Albertini 2013; Brooks and Theruvathu 2005; IARC 1999). Acetaldehyde reacts directly with the exocyclic amino group of deoxyguanosine (dG) to form DNA adducts such as N^2-ethylidene-2'-deoxyguanosine (N^2-ethylidene-dG or N^2-Etd-dG)[13], N^2-propano-dG [14], and N^2-ethano-2'-deoxyguanosine (NεG) (Mizumoto et al. 2017). The N^2-Etd-dG adduct is very unstable and is further reduced to N^2-Ethyl-dG, which is the most well-known and best-studied of the acetaldehyde-DNA lesions (Brooks and Theruvathu 2005). While most studies focus on acetaldehyde and dG adducts, one study indicated that acetaldehyde can interact with other bases. Vaca et al. (1995) reported the formation of very unstable deoxyadenosine (dA) and deoxycytidine (dC) acetaldehyde adducts by incubating acetaldehyde with deoxynucleosides in solutions under neutral pH (Vaca et al. 1995). However, the authors could not characterize the structures of these adducts due to their unstable nature.

Summary

While only a few studies have investigated the electrophilicity of vinyl acetate, by measuring DNA adducts, the evidence for the electrophilicity of the vinyl acetate metabolite acetaldehyde is robust. The available data show that exposure to vinyl acetate, like its metabolite acetaldehyde, can result in the formation of DNA adducts.

5.2.2 Is genotoxic (KC2)

Genotoxicity refers to the ability of a chemical or other type of agent or biological process to damage DNA or induce changes in the DNA sequence. The link between genotoxicity and carcinogenesis is well established (Smith et al. 2016; Smith et al. 2020). Changes in the DNA sequence include gene or point mutations such as base

[13] According to Hsiao et al. (2022), N^2-EtD-dG is not stable and requires chemical reduction into stable N2-ethyl-dG (N2-Et-dG) for detection.
[14] Mizumoto et al. (2017) referred to this adduct as α-*S*- and α-*R*-methyl-γ-hydroxy-1, N^2-propano-2'-deoxyguanosine, with the abbreviation CrpdG, highlighting isomerization possibilities. This is the same adduct as 1,N^2-propano-deoxyguanosine (1,N^2-PdG, or N^2-propano-dG).

substitutions, frameshifts, and small deletions or insertions, and chromosomal effects such as chromosomal aberrations, micronuclei, and aneuploidy. Examples of DNA damage include DNA adducts, DNA strand breaks, and oxidative damage to DNA.

OEHHA conducted a literature search on genotoxicity of vinyl acetate, and the identified references are similar to those reviewed by IARC (1995) and ATSDR in its draft toxicological profile (ATSDR 2023). An additional review by Albertini (2013) on the genotoxicity of vinyl acetate and its metabolite acetaldehyde was also identified in the literature search. Only one study, from Hsiao et al. (2022) on DNA adduct formation in exposed rats, was identified by OEHHA that was not already cited in the above reviews.

In its 1995 evaluation, IARC stated that both "vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*."

Here, we summarize the genotoxicity findings from studies of vinyl acetate by test system and endpoint. We also briefly summarize genotoxicity findings from studies of vinyl acetate's genotoxic and carcinogenic metabolite, acetaldehyde. Vinyl acetate genotoxicity study details are presented in Table 29–30.

Human observational genotoxicity studies of vinyl acetate

- Increased levels of chromosomal aberrations (CAs) were reported in the lymphocytes of polyvinyl acetate manufacturing workers in 1976, 1977, and 1978 (n = 19, 27, 27, respectively), compared to non-chemical industry workers in 1978 (n = 20) in a study published in Russian (Shirinian and Arutyunyan 1980).[15]

Genotoxicity studies of vinyl acetate in human cells in vitro

Mutagenicity

- Vinyl acetate induced mutations at the *Thymidine kinase (TK)* locus but not the *HPRT* locus, in human TK6 lymphoblastoid cells. The vinyl acetate-induced mutant frequency at the *TK* locus was greater in TK6 cells cultured in medium with higher levels of carboxylesterase-like activity[16] (medium supplemented with heat-inactivated horse serum (HS)), as compared to cells cultured in non-supplemented medium, or in medium supplemented with heat-inactivated fetal bovine serum (FBS) (Budinsky et al. 2013).

[15] OEHHA reviewed the study in Russian. For data on chromosomal aberrations, see Table 1 of Shirinian and Arutyunyan (1980). This study was also reviewed by Albertini (2013).
[16] Vinyl acetate underwent rapid and nearly complete hydrolysis to acetaldehyde within 60 minutes in RPMI medium supplemented with heat-inactivated HS under cell-free conditions. Hydrolysis was considerably less (ranging from 5-11%) in non-supplemented medium and in medium supplemented with heat-inactivated FBS (Budinsky et al. 2013).

- Direct exposure to acetaldehyde was also shown to induce mutations in TK6 cells at the *TK* but not the *HPRT* locus (Budinsky et al. 2013).

Chromosomal Effects

Micronuclei (MN) Formation

- Significant induction of MN by vinyl acetate in cultured human whole blood lymphocytes (Mäki-Paakkanen and Norppa 1987).
- Significant induction of MN by vinyl acetate in human TK6 lymphoblastoid cells cultured in medium supplemented with heat-inactivated HS and assessed at four hours (this culture medium was shown to have robust carboxylesterase-like activity). No increase of MN when tested with medium supplemented with heat-inactivated FBS after 4 or 24 hours treatment (Budinsky et al. 2013).
    - Direct exposure to acetaldehyde was also shown to increase MN in TK6 cells cultured in medium supplemented with either heat-inactivated HS or FBS (Budinsky et al. 2013).

Chromosomal Aberrations (CAs)

- Statistically significant induction of CAs by vinyl acetate reported in:
    - First division cells of human whole blood cultures and cultures of isolated lymphocytes in a dose-dependent manner (Norppa et al. 1985).
    - Human whole blood cultures and isolated lymphocytes (significant increase in chromatid-type aberrations and a slight elevation in chromosome-type breaks) (Jantunen et al. 1986).
    - Human peripheral lymphocytes (with statistically significant induction of chromatid aberrations, including breaks and gaps) (Mustonen et al. 1986).

Sister Chromatid Exchange (SCE)

- Statistically significant increases in SCE by vinyl acetate were observed in:
    - Human lymphocytes in both early and late-stage cell cycle, in a dose-dependent manner (He and Lambert 1985).
    - Human whole blood cultures and isolated lymphocytes (Norppa et al. 1985).
        - Direct exposure to acetaldehyde also increased SCEs (Norppa et al. 1985).
    - Human whole blood lymphocyte cultures (Sipi et al. 1992).

DNA damage

- No increase of DNA strand breaks was observed in human leucocytes treated with vinyl acetate for 4 hours (Lambert et al. 1985).

    - No increase of DNA strand breaks was observed with acetaldehyde treatment (Lambert et al. 1985).
- Increased DNA crosslinks (type not specified) in cultured human leucocytes, as measured by slower elution (due to bulky cross-links) in cells exposed to vinyl acetate and X-ray irradiation compared to X-ray irradiation alone (Lambert et al. 1985).
    - Acetaldehyde treatment also increased DNA cross-links at 10 mM, followed by 5 Gy of X-irradiation (Lambert et al. 1985).

Genotoxicity studies of vinyl acetate in laboratory animals

Chromosomal Effects

Micronuclei (MN) Formation

- Significant induction of MN by vinyl acetate in:
    - Bone marrow erythrocytes of male C57Bl/6 mice after a single *i.p.* injection (Mäki-Paakkanen and Norppa 1987).
    - Bone marrow of male Fischer 344 rats after three *i.p.* injections administered over 48 hr, followed by 24 hr of observation prior to cell sampling (NTP 2017b).
- Incidence of MN was higher in bone marrow erythrocytes of male CD-1 mice exposed to high-dose vinyl acetate via drinking water for 4 weeks compared to control mice, although the counts were within the expected spontaneous range of occurrence; no increase of MN in similarly treated female CD-1 mice (Gale 1979).
- No induction of MN by vinyl acetate in:
    - Bone marrow erythrocytes of male or female Sprague-Dawley derived rats of the CD strain or CD-1 mice exposed to vinyl acetate via inhalation for 3 or 13 weeks (Owen 1979a, b, 1980a, b).
    - Bone marrow erythrocytes in male or female rats (Sprague-Dawley derived rats of the CD strain) or CD-1 mice exposed orally via drinking water for 4 or 13 weeks (Gale 1979, 1980a, b).
    - Spermatogonial cells of male (C57B1/6J x C3H/He)F_1 mice following single *i.p.* injection (Lähdetie 1988).
        - Acetaldehyde treatment also did not induce MN formation (Lähdetie 1988).

CAs

- Increased CAs by vinyl acetate in bone marrow cells of male Wistar rats after a single *i.p.* injection [(Nersesyan et al. 1990), as reviewed by (Albertini 2013)].

SCE

- Increased SCE by vinyl acetate in bone marrow cells of male BDF mice following a single *i.p.* injection (Takeshita et al. 1986).

DNA damage[17]

- Treatment-related [$13C_2$]-N2-Ethyl-dG DNA adducts detected via sensitive LC-MS/MS in nasal respiratory and olfactory epithelia and peripheral blood mononuclear cells (PBMCs) of rats treated with [$^{13}C_2$]-vinyl acetate via inhalation for 6 hr. [$13C_4$]-N2-propano-dG DNA adducts were detected in nasal the respiratory epithelia of rats exposed to 400 ppm [$^{13}C_2$]-vinyl acetate, although these adducts were present at lower levels in these animals than [$^{13}C_2$]-N^2-Ethyl-dG (Liu et al. 2021).
- Treatment-related [$13C_2$]-N2-Ethyl-dG DNA adducts detected in nasal epithelia of rats treated with [$^{13}C_2$]-vinyl acetate via inhalation for 6 hr/day for 14 days. Low amounts of [$13C_2$]-N2-Ethyl-dG adducts were also detected in one of three pooled samples of PBMCs of rats exposed to 50 ppm [$13C_2$]-vinyl acetate. No vinyl acetate-derived adducts were detected in the liver, brain, or bone marrow of exposed rats (Hsiao et al. 2022).
- No vinyl halides or vinyl carbamate-associated DNA adducts detected via HPLC in hepatocytes of rats exposed to ^{14}C-vinyl acetate via inhalation or a single oral dose (Simon et al. 1985b).

Genotoxicity studies of vinyl acetate in animal cells in vitro

Mutagenicity

- In the L5178Y mouse lymphoma cell line, vinyl acetate treatment increased the mutant frequencies of the *TK* locus in the presence and absence of S9 [Kirby (1983), as reviewed by Albertini (2013) and ECHA (2008)].[18]

Chromosomal Effects

SCE

- Significant increase in SCE by vinyl acetate in Chinese hamster ovary (CHO) cells with and without S9 (Norppa et al. 1985).

[17] See Section 5.2.1 (KC1) for more details on each of the three studies discussed here.
[18] OEHHA could not access the full Kirby (1983) report and relied on the two reviews. Albertini (2013) and ECHA (2008) discussed limitations of this study, including lack of colony sizing, high vinyl acetate concentrations used, and more.

DNA damage

- Induction of DNA-protein crosslinks by vinyl acetate in rat nasal epithelial cells, which was blocked by addition of a carboxylesterase inhibitor (Kuykendall et al. 1993).

Bacterial and acellular systems

Mutagenicity

- No mutagenic activity was reported for vinyl acetate in tests conducted in multiple *S. typhimurium* strains and two *E. coli* strains[19] (Bartsch 1976; Bartsch et al. 1979; Brams et al. 1987; Emmert et al. 2006; Florin et al. 1980; IARC 1976; JETOC 2004; Jung et al. 1992; Lijinsky and Andrews 1980; McCann et al. 1975; Muller et al. 1993; NTP 2017a; Watanabe et al. 1998).

DNA damage

- DNA-protein crosslinks were formed by incubation of ^{3}H-labeled pUC13 plasmid DNA and calf thymus histones with vinyl acetate in the presence of rat liver microsomes; results were negative in the absence of microsomes (Kuykendall and Bogdanffy 1992).

Genotoxicity of acetaldehyde

Acetaldehyde, one of vinyl acetate's metabolites, is listed under Proposition 65 as a carcinogen, and it is a known genotoxicant in both *in vitro* and *in vivo* assays. IARC has classified acetaldehyde as a Group 2B carcinogen since 1987 (IARC 1987, 1999).[20] For a detailed review of the genotoxicity profile for acetaldehyde, see IARC (1999), IARC (2010) and IARC (2012) and for a comparison with vinyl acetate, the reader is directed to Albertini (2013). General similarities between the genotoxicity of vinyl acetate and acetaldehyde will be shared here.

Although a paucity of data exists regarding vinyl acetate and mutagenicity in human or other mammalian systems [(Budinsky et al. 2013) and (Kirby 1983), as reviewed by Albertini (2013) and ECHA (2008)], several studies of acetaldehyde and mutagenicity have been conducted, and as reviewed by Albertini (2013), they show positive results for increased *TK, HPRT, and TP53* mutations after acetaldehyde exposure in human and mammalian cells. With regard to mutagenicity in bacteria, vinyl acetate and acetaldehyde show virtually the same pattern; acetaldehyde was negative in all bacteria

[19] Vinyl acetate was tested in the following bacterial strains (in most cases both with and without metabolic activation): *Salmonella* strains TA97, TA98, TA100, TA102, TA1530, TA1535, TA1537, TA1538, TA2638, and YG7108pin3ERb$_5$, and *E coli* strains WP2/pKM101 and WP2 uvrA/pKM101.
[20] IARC (2012) classifies "acetaldehyde associated with the consumption of alcoholic beverages" as carcinogenic to humans (Group 1). IARC (2010) is an earlier IARC monograph on consumption of alcoholic beverages, with information on genotoxicity of acetaldehyde.

assays except for one in *E. coli* (Veghelyi et al. 1978). Acetaldehyde also induced mutations in the fungus *Aspergillus nidulans* (Albertini 2013; Crebelli et al. 1989).

An overwhelming amount of positive data for chromosomal damage exists for acetaldehyde; *in vitro* studies have consistently shown acetaldehyde to cause MN, CAs, and SCE (IARC 2010). Acetaldehyde led to a significant induction of MN in human TK6 lymphoblastoid cells. Such effects were also observed in cells treated with vinyl acetate, but only when the culture medium was supplemented with heat-inactivated horse serum, which was capable of hydrolyzing vinyl acetate to form acetaldehyde (Budinsky et al. 2013). Equimolar doses of vinyl acetate and acetaldehyde were shown to have similar effects and dose response for SCE in human lymphocytes (He and Lambert 1985). Studies with knockout mice indicate that acetaldehyde's *in vivo* genotoxicity (chromosomal damage and mutagenicity) appears to be influenced by *ALDH2* status. Studies in *Aldh2* deficient knockout mice have demonstrated the role ALDH2 plays in protecting against acetaldehyde-induced genotoxicity. Specifically, MN and T-cell receptor gene mutations were increased in *Aldh2* deficient knockout mice after inhalation or oral exposure to acetaldehyde for 14 days (Kunugita et al. 2008).

Acetaldehyde has been shown to increase DNA strand breaks *in vitro* in several cell types, and unscheduled DNA synthesis (UDS) *in vitro* in rat hepatocytes (Albertini 2013). While vinyl acetate has not been shown to induce DNA strand breaks, OEHHA did not identify any studies investigating its effect on UDS. Acetaldehyde has been shown to form DNA adducts, DNA-DNA crosslinks, and DNA-protein crosslinks in cell free systems, *in vitro* in human and non-human mammalian cells, and *in vivo* in rodents (Albertini 2013; IARC 2010). Importantly, the acetaldehyde-DNA adducts have been demonstrated to be either directly mutagenic or lead to formation of DNA-protein crosslinks and DNA interstrand crosslinks *in vitro* and *in vivo* (Brooks and Theruvathu 2005). Vinyl acetate has been shown to form two of these same DNA adducts (*e.g.,* N2-Ethyl-dG, N2-propano-dG) in two rodent studies *in vivo*, and DNA-protein crosslinks in animal cells *in vitro* and in cell-free systems (Hsiao et al. 2022; Liu et al. 2021).

Summary

Vinyl acetate induces MN (human cells *in vitro* and animals *in vivo*), CA (human cells *in vitro* and animals *in vivo*), SCE (animals *in vivo* and human and animal cells *in vitro*), DNA adducts (animals *in vivo*), and DNA-protein crosslinks (animal cells *in vitro* and a cell-free system). In *in vitro* studies, vinyl acetate is genotoxic at non-cytotoxic concentrations (see Table 30). The genotoxicity findings for vinyl acetate are consistent with and supported by those seen in studies of its metabolite, acetaldehyde.

Table 29. Vinyl acetate *in vivo* genotoxicity studies in humans and other mammals

End-point	Species, strain, sex, tissue, cell type	Route, duration, dosing regimen, dose range	Dose (LED or HID)[21]	Results	Comments	Reference
Chromosomal aberrations (CAs)	Human, lymphocytes	Occupational exposure	N/A	+	Study in Russian. As Albertini (2013) points out, few details are available regarding confounding and other factors.	Shirinian and Arutyunyan (1980)
Micronuclei (MN)	Mouse, C57BL/6, male, bone marrow erythrocytes	*i.p.* injection, single, 0, 250, 500, 1000, 2000 mg/kg bw	1000 mg/kg bw	+	Animal termination and slides preparation occurred 30 hr after injection. Findings were dose dependent. 6/14 and 8/14 animals died from the 1000 and 2000 mg/kg dose groups, respectively.	Mäki-Paakkanen and Norppa (1987)
MN	Mouse, (C57B1/6J x C3H/He)F1, male, spermatogonial cells	*i.p.* injection, single, 0, 250, 500, 750, 1000 mg/kg/d	1000 mg/kg	–	Animal termination and sample collection occurred 13 days after injection. Acetaldehyde treatment also did not cause any change in MN formation.	Lähdetie (1988)
MN	Mouse, CD-1, male and female, bone marrow erythrocytes	Inhalation, 6 hr/d, 5 d/wk, 3 wks, 0, 50/1500, 150, 500, 1000 ppm v/v	1500 ppm v/v	–	Mice originally assigned to the 50 ppm group were increased to 1,500 ppm v/v on exposure day 8 as a result of the 1000 ppm v/v group showing no clinical effects at the time. At	Owen (1979b)

[21] LED: lowest effective dose; HID: highest ineffective dose.

End-point	Species, strain, sex, tissue, cell type	Route, duration, dosing regimen, dose range	Dose (LED or HID)[21]	Results	Comments	Reference
					concentrations of 150 ppm and above vinyl acetate appeared to be a respiratory irritant.	
MN	Mouse, CD-1, male and female, bone marrow erythrocytes	Inhalation, 6 hr/d, 5 d/wk, 13 wks, 0, 50, 200, 1000 ppm v/v	1000 ppm v/v	–	200 and 1000 ppm vinyl acetate appeared to be a respiratory irritant.	Owen (1980a)
MN	Mouse, CD-1, male and female, bone marrow erythrocytes	Oral (drinking water), 4 wks, 0, 50/10000, 150, 1000, and 5000 ppm v/v	5000 ppm v/v	+ in one group of male mice; – in female mice	Positive MN results for male mice in the 5000 ppm group and negative for the remaining groups. During the last week of treatment, animals receiving 50 ppm were offered drinking water containing vinyl acetate at 10000 ppm.	Gale (1979)
MN	Mouse, CD-1, male and female, bone marrow erythrocytes	Oral (drinking water), 13 wks, 0, 200, 1,000, and 5,000 ppm v/v	5000 ppm v/v	–	Water consumption was lower in high and intermediate doses (except intermediate females); higher water wastage was also observed in these animals indicating a possible unpalatability of the vinyl acetate treated water.	Gale (1980a)
MN	Rat, CD, male and female, bone marrow	Inhalation, 6 hr/d, 5 d/w, 4 wks, 0, 50/1500. 150, 500,	1000 ppm v/v	–	Vinyl acetate ≥ 500 ppm appeared to be a respiratory irritant (incidence of	Owen (1979a)

End-point	Species, strain, sex, tissue, cell type	Route, duration, dosing regimen, dose range	Dose (LED or HID)[21]	Results	Comments	Reference
	erythrocytes	1000 ppm v/v			respiratory distress and hunched posture reported). A dose-related decrease in BW was reported. The 1000 ppm female dose group had a significantly greater myeloid/erythroid ratio compared to controls.	
MN	Rat, CD, male and female, bone marrow erythrocytes	Inhalation, 6 hr/d, 5 d/wk, 13 wks, 0, 50, 200, and 1000 ppm v/v	1000 ppm v/v	–	1000 ppm dose appeared to be a respiratory irritant. At 1000 ppm, vinyl acetate caused a decrease in BW.	Owen (1980b)
MN	Rat, CD, male and female, bone marrow erythrocytes	Oral (drinking water), 4 wks, 0, 50/10000, 200, 1000, and 5000 ppm v/v	5000 ppm v/v	–	During the last week of treatment, animals receiving 50 ppm had their dose increased to 10000 ppm. Water consumption was lower in animals exposed to 10000 and 5000 ppm, and in females treated at 1000 ppm.	Gale (1979)
MN	Rat, CD, male and female, bone marrow erythrocytes	Oral (drinking water), 13 wks, 0, 200, 1000, and 5000 ppm v/v	5000 ppm v/v	–	Water consumption was lower in 5000 and 1000 ppm treatment groups (except 1000 ppm females).	Gale (1980b)
MN	Rat, Fischer 344, male, bone marrow erythrocytes	*i.p.* injection, 3 days with bone marrow sampling 24 hr after the third treatment, 0,	375 mg/kg	+	Study initiated on 09/27/1994	NTP (2017b)

End-point	Species, strain, sex, tissue, cell type	Route, duration, dosing regimen, dose range	Dose (LED or HID)[21]	Results	Comments	Reference
		93.75, 187, 375, 750, 1500 mg/kg				
MN	Rat, Fischer 344, male, bone marrow erythrocytes	*i.p.* injection, 3 days with bone marrow sampling 24 hr after third treatment, 0, 250, 500, 750 mg/kg	500 mg/kg	+	Study initiated on 02/09/1999	NTP (2017b)
CAs	Rat, Wistar, male, bone marrow cells	*i.p.* injection, single, 160 mg/kg	N/A	+	Chromosomal aberration frequency was 8.2% compared to 0.6% in negative controls. Original study in Armenian and the English summary was reviewed by Albertini, 2013, who considered the study to be of low reliability.	Nersesyan et al. (1990), summary reviewed by Albertini (2013)
Sister Chromatid Exchange	Mouse, BDF, male, bone marrow cells	*i.p.* injection, 0, 370, 470, 560 mg/kg	370 mg/kg	+	Dose-related increase; increase observed in bone marrow cells of both hepatectomized and non-hepatectomized mice.	Takeshita et al. (1986)
DNA adducts	Rat, Fischer-344, male and female; Wistar, male; hepatic tissue	Oral (gavage), [Vinyl-U-^{14}C]vinyl acetate, animals measured 4 hr after dosing, 1 mCi radioactive vinyl acetate	N/A	–	Animals were killed 4 hours after treatment. The authors did not observe detection of any known DNA adducts of vinyl halides or vinyl carbamate.	Simon et al. (1985b)
DNA adducts	Rat, Fischer-344, male and female;	Inhalation, [Vinyl-U-^{14}C]vinyl acetate,	N/A	–	Animals were killed 4 hours after treatment. Initial	Simon et al. (1985b)

End-point	Species, strain, sex, tissue, cell type	Route, duration, dosing regimen, dose range	Dose (LED or HID)[21]	Results	Comments	Reference
	Wistar, male; hepatic tissue	animals measured 4 hr after dosing, 2.9-4.9 mCi radioactive vinyl acetate			concentration in the chamber ranged from 1200-1800 ppm and after 90 min, dropped below 1 ppm. The authors did not observe detection of any known DNA adducts of vinyl halides or vinyl carbamate.	
DNA adducts	Rat, Sprague-Dawley, male, nasal respiratory and olfactory epithelia, and peripheral blood mononuclear cells (PBMCs)	Inhalation, 6 hr, [$^{13}C_2$]-vinyl acetate monomer. Rats were sacrificed at 0, 6, 12, 24, 48, and 120 hr postexposure, 0, 50, 200, 400 ppm	50 ppm	+ (nasal tissues and PBMCs)	Dose-dependent increases of exogenous N2-ethyl-dG adducts. Twice as many exogenous N2-ethyl-dG adducts were found in the nasal respiratory epithelium than olfactory epithelium.	Liu et al. (2021)
DNA adducts	Rat, Sprague-Dawley, male, nasal respiratory and olfactory epithelia, PBMCs, liver, brain, and bone marrow	Inhalation, 6 hr/d, 14 days exposure to [$^{13}C_2$]-vinyl acetate, 0, 0.2, 0.1, 1, 10, 50, 200, 600 ppm	10 ppm	+ (nasal tissues) ± (PBMCs) – (liver, brain, and bone marrow)	Unlabeled vinyl acetate was used for the 200 and 600 ppm exposure groups. N2-Ethyl-dG adduct was identified as the primary exogenous DNA adduct induced by vinyl acetate exposure. Exogenous N2-Ethyl-dG was detected in 1 of 3 pooled replicates of PBMC samples. No exogenous DNA adducts were detected in liver, brain, or bone marrow of treated rats.	Hsiao et al. (2022)

Table 30. Vinyl acetate genotoxicity studies in human and other mammalian cells *in vitro* or in cell-free systems

Endpoint	Species, cell type	Concentration Range	Concentration (LEC or HIC)[22]	Results	Comments	Reference
Mutations	Human, cultured TK6 lymphoblast cells	0.001–4 mM	0.25 mM	+ (*TK* locus) – (*HPRT* locus)	24-hr treatment; cells were cultured in heat-inactivated horse serum (high capacity for hydrolysis); cytotoxicity appears to be moderate at 0.25 mM (64% cell survival). Acetaldehyde increased mutation frequency of *TK* locus at 0.05 mM. No increases were observed at the *HPRT* locus with either vinyl acetate or acetaldehyde.	Budinsky et al. (2013)
Mutations	Human, cultured TK6 lymphoblast cells	0.001–4 mM	0.25 mM with fetal bovine serum (FBS) 0.5 mM without FBS	+ (*TK* locus)	24-hr treatment; cells were cultured with or without heat-inactivated FBS (low capacity for hydrolysis); cytotoxicity appears to be moderate at 0.25 mM (63% cell survival) and minimal at 0.5 mM (85% cell survival). The authors mentioned briefly that acetaldehyde caused a higher increase of mutation frequency than vinyl acetate.	Budinsky et al. (2013)
Mutations	Mouse, L5178Y	20.547–43.256 mM	20.547 mM	+	Without S9	Kirby (1983), as reviewed by

[22] LEC: lowest effective concentration; HIC: highest ineffective concentration.

Endpoint	Species, cell type	Concentration Range	Concentration (LEC or HIC)[22]	Results	Comments	Reference
	lymphoma cells					(Albertini 2013) and ECHA (2008)
Mutations	Mouse, L5178Y lymphoma cells	19.465–54.070 mM	19.465 mM	+	With S9	Kirby (1983), as reviewed by Albertini (2013) and ECHA (2008)
Micronuclei (MN)	Human, whole blood cultures	0.125–2 mM	0.5 mM	+	48-hr treatment starting at 24-hr after culture initiation; 2 mM appeared to be toxic.	Mäki-Paakkanen and Norppa (1987)
MN	Human, cultured TK6 lymphoblast cells	0.001–2 mM	0.25 mM	+	4-hr treatment; cells were cultured in heat-inactivated horse serum (high capacity for hydrolysis); cytotoxicity appears to be minimal at 0.25 mM (94% cell survival) and minor at 0.5 mM (73% cell survival). Acetaldehyde also increased MN starting at 0.25 mM.	Budinsky et al. (2013)
MN	Human, cultured TK6 lymphoblast cells	0.001–2 mM	2 mM	–	4-hr treatment; cells were cultured in heat-inactivated FBS (low capacity for hydrolysis of vinyl acetate). Acetaldehyde increased MN	Budinsky et al. (2013)

Endpoint	Species, cell type	Concentration Range	Concentration (LEC or HIC)[22]	Results	Comments	Reference
					starting at 0.25 mM.	
MN	Human, cultured TK6 lymphoblast cells	0.001–2 mM	2 mM	–	24-hr treatment; cells were cultured in heat-inactivated FBS (low capacity for hydrolysis). Acetaldehyde increased MN starting at 0.25 mM.	Budinsky et al. (2013)
Chromosomal aberrations (CAs)	Human, whole-blood cultures	0.05–1 mM	0.5 mM	+	48-hr treatment	Norppa et al. (1985)
CAs	Human, isolated lymphocytes	0.05–1 mM	0.2 mM	+	48-hr treatment	Norppa et al. (1985)
CAs	Human, whole-blood cultures	0.125–2 mM	0.25 mM	+	24-hr treatment starting at 48-hr after culture initiation, 100 metaphases from duplicate culture (200 metaphases/treatment). Treatment effect appears dose dependent, no trend test reported.	Jantunen et al. (1986)
CAs	Human, isolated lymphocytes	0.125–2 mM	0.25 mM	+	24-hr treatment starting at 48-hr after culture initiation, 100 metaphases from duplicate culture (200 metaphases/treatment). Treatment effect appears dose dependent, no trend test reported.	Jantunen et al. (1986)
CAs	Human,	0.5 mM	0.5 mM	+	Vinyl acetate was used as a	Mustonen et

Endpoint	Species, cell type	Concentration Range	Concentration (LEC or HIC)[22]	Results	Comments	Reference
	isolated lymphocytes				positive control; 24-hr treatment.	al. (1986)
Sister Chromatid Exchange (SCE)	Human, isolated lymphocytes	0.1–0.3 mM	0.1 mM	+	Vinyl acetate was added immediately after PHA stimulation (early G1 phase) or 20-23 hr later (late G1 phase); cells were harvested after 70 hr.	He and Lambert (1985)
SCE	Human, isolated lymphocytes	0.6–2.4 mM	0.6 mM	+	Vinyl acetate was added during a 1-hr period in the early G1 phase (0-1 hr), removed, and added again during the late G1 phase (23-24 hr).	He and Lambert (1985)
SCE	Human, whole-blood cultures	0.05–1 mM	0.1 mM	+	48-hr treatment; Effects were dose-dependent; cell proliferation index remained over 90% at 0.1 and 0.2 mM vinyl acetate, vinyl acetate appeared to be cytotoxic at ≥0.5 mM. Acetaldehyde also increased SEC after 48-hr treatment in a dose-dependent manner.	Norppa et al. (1985)
SCE	Human, isolated lymphocytes	0.05–1 mM	0.05 mM	+	48-hr treatment; cell proliferation index remained over 85% at 0.05 and 0.1 mM vinyl acetate, vinyl acetate appeared to be cytotoxic at ≥0.2 mM.	Norppa et al. (1985)

Endpoint	Species, cell type	Concentration Range	Concentration (LEC or HIC)[22]	Results	Comments	Reference
SCE	Human, whole blood lymphocytes	0.25–1 mM	0.25 mM	+	48-hr treatment; vinyl acetate was included as a positive control; 0.25 mM vinyl acetate did not decrease replication index	Sipi et al. (1992)
SCE	Hamster, ovary cells (Chinese Hamster Ovary or CHO cells)	0.125–2 mM	0.125 mM	+	24-hr treatment	Norppa et al. (1985)
SCE	Hamster, ovary cells (CHO)	0.31–5 mM	0.31 mM	+	4-hr treatment in serum-less media, then rinsed and recovered in complete medium for 24-hr. Treatment appeared cytotoxic at 5 mM without S9.	Norppa et al. (1985)
SCE	Hamster, ovary cells (CHO)	0.31–5 mM	0.31 mM	+	S9 mix (derived from the livers of Wistar rats induced with Aroclor 1254) added to sealed, 4-hr treatment in serum-less media, then rinsed and recovered in complete medium for 24-hr. Treatment appeared cytotoxic at 1.25 mM.	Norppa et al. (1985)
DNA strand breaks	Human, cultured leucocytes	10 or 20 mM	20 mM	–	4-hr treatment. No effects were seen with acetaldehyde at 10 mM.	Lambert et al. (1985)
DNA cross-	Human, cultured	10 or 20 mM	10 mM	+	4-hr treatment, followed by 5 Gy of	Lambert et al.

Endpoint	Species, cell type	Concentration Range	Concentration (LEC or HIC)[22]	Results	Comments	Reference
links	leucocytes				X-irradiation. Acetaldehyde also increased DNA cross-links at 10 mM, followed by 5 Gy of X-irradiation.	(1985)
DNA-protein cross-links	Rat, nasal epithelial cells	5–75 mM	5 mM	+	1 or 2-hr treatment; vinyl acetate was cytotoxic ≥ 50 mM	Kuykendall et al. (1993)
DNA-protein cross-links	Cell-free, pUC13 plasmid DNA, calf thymus histones	1–100 mM	1 mM	+	1–3 hr-treatment with added rat liver microsomes.	Kuykendall and Bogdanffy (1992)
DNA-protein cross-links	Cell-free, pUC13 plasmid DNA, calf thymus histones	1–100 mM	100 mM	–	1–3 hr-treatment with rat liver microsomes and a carboxylesterase inhibitor.	Kuykendall and Bogdanffy (1992)

5.2.3 Alters cell proliferation, cell death or nutrient supply (KC10)

As reviewed in Smith et al. (2016) and Smith et al. (2020), carcinogens may alter cell cycle control, stimulate uncontrolled cell proliferation and angiogenesis to increase vascularity, and enable the evasion of apoptosis. Examples of effects indicative of KC10 include increased cell proliferation and hyperplasia, decreased apoptosis, changes in growth factors, changes in energetics and signaling pathways related to cellular replication or cell cycle control, and increased angiogenesis.

This section discusses KC10-related findings from studies of vinyl acetate conducted in rats and mice *in vivo* that assessed cell proliferation, hyperplasia, or dysplasia.[23] For a more detailed review of the tumor findings in the same tissues where cell proliferation, hyperplasia or dysplasia were seen, see Sections 4.1 and 4.2.

Cell proliferation (from in vivo rodent studies)

Rats

- Male Crl:CD BR rats exposed to vinyl acetate (0, 50, 200, 600, or 1000 ppm) via inhalation for 1, 5, or 20 exposures (6 hours/day for up to 4 weeks, excluding weekends) were evaluated for nasal cavity cellular proliferation using the 5-bromo-2'-deoxyuridine (BrdU) pulse label method. In the nasal respiratory epithelium, concentrations of 600- and 1000-ppm vinyl acetate caused a significant increase in cell proliferation when measured after a single exposure. Cell proliferation was not statistically significantly increased when measured after 5 and 20 exposures. In the nasal olfactory epithelium, significant increases of cell proliferation were seen after a single exposure or 20 exposures of 600- or 1000-ppm vinyl acetate, but not after 5 exposures, or after any number of exposures in the 50- or 200-ppm groups (Bogdanffy et al. 1997).
- Vinyl acetate was administered in drinking water (0, 1000, 5000, 10000 or 24000 ppm) for 92 days (slightly over 13 weeks) to male CDF®(F-344)/CrlBr rats. On days 1, 8, 29, and 92, oral cavity cellular proliferation was evaluated only in the control and high-dose groups, using the BrdU pulse label method. There was a statistically significant increase in cellular proliferation in the oral cavity maxillary mucosa on days 29 and 92 and in the oral cavity mandibular mucosa on days 1

[23] Dysplasia is a more advanced condition than hyperplasia and is considered by pathologists to be a preneoplastic lesion. Dysplasia is characterized by disordered growth and abnormal proliferation, and the cells have a distinctly abnormal and variable appearance (LaMorte 2016; Maronpot 2015). Squamous cell dysplasia is a form of epithelial proliferation (Leininger and Jokinen 1994).

and 29 in the high-dose group, compared to controls (Valentine et al. 2002). The authors did not evaluate the remaining treatment groups.

Mice

- Vinyl acetate was administered in drinking water (0, 1000, 5000, 10000 or 24000 ppm) for 92 days (a little over 13 weeks) to male B6D2F1/CrlBr mice. On days 1, 8, 29, and 92, oral cavity cellular proliferation was evaluated using the BrdU pulse label method in control and high-dose mice; remaining treatment groups were only evaluated on day 92. On day 92, statistically significant and concentration-related increases in cellular proliferation in basal cells of the mandibular oral cavity mucosa were observed in mice treated with 10000- and 24000-ppm vinyl acetate, compared to controls (Valentine et al. 2002).

Hyperplasia and dysplasia (from in vivo rodent studies)

Rats

- In studies of male and female Wistar rats, F_0 animals were administered 0, 1000, or 5000 ppm of vinyl acetate in drinking water for 104 weeks and F_1 animals were exposed to 0, 1000, or 5000 ppm of vinyl acetate *in utero*, through lactation, and post weaning in drinking water (*ad libitum*) for up to 104 weeks. All animals then received tap water until natural death. Tissues were examined for histopathology. In F_1 males, a statistically significant increase in squamous cell dysplasia of the esophagus was observed in the 5000-ppm dose group compared to controls. In F_0 females, a statistically significant increase in squamous cell dysplasia of the esophagus was observed in the 5000-ppm dose group compared to controls. In F_1 females, statistically significant increases in squamous cell dysplasia of the oral cavity and esophagus were observed in the 5000 ppm dose group compared to controls (Belpoggi et al. 2002).
- In inhalation studies of male and female Sprague-Dawley-derived rats (Crl:CD BR), animals were exposed to vinyl acetate (0, 50, 200, or 600 ppm) for 104 weeks. Tissues were examined for histopathology. Statistically significant increases in basal cell hyperplasia of the nasal olfactory epithelium were observed in males and females in the 200- and 600-ppm dose groups, compared to the respective controls (Bogdanffy et al. 1994a).
- In studies of male and female F344 rats, animals were treated with 0, 1000, or 2500 ppm vinyl acetate in drinking water for two years. Tissues were examined for histopathology. In females a statistically significant increase in thyroid gland C-cell hyperplasia was observed at the low dose compared to controls (EPL 1982).

- In studies of male and female F344/DuCrj rats, animals were orally administered vinyl acetate (0, 400, 2000, or 10000 ppm) in drinking water for 104 weeks. Macroscopic and histopathological examinations were performed on all animals. In males, 2/50 male rats in the high-dose group had basal cell activation[24] in the oral cavity, compared to none in the other groups. In females, a significant increase in basal cell activation of the stomach was observed in the 10000-ppm group, compared to controls. One female rat in the 10000-ppm group had basal cell activation in the oral cavity, compared to none in the other groups (JBRC 1995; Umeda et al. 2004).
- In studies of male and female Sprague-Dawley rats, F_0 animals were administered 0, 1000, or 5000 ppm of vinyl acetate in drinking water for 104 weeks and F_1 animals were administered 0, 1000, or 5000 ppm of vinyl acetate *in utero*, through lactation, and post weaning in drinking water for up to 104 weeks. In F_1 males, statistically significant increases in squamous cell dysplasia of the esophagus in the 5000-ppm group and of the forestomach in the 1000 and 5000 ppm groups were observed compared to controls. In F_0 females, statistically significant increases in squamous cell dysplasia of the tongue, esophagus, and forestomach were observed in the 5000-ppm group compared to controls. In F_1 females, statistically significant increases in squamous cell dysplasia of the tongue and esophagus (5000-ppm group) and of the forestomach (1000- and 5000-ppm groups) were observed compared to controls (Minardi et al. 2002).

Mice

- In inhalation studies of male and female Crl:CD-1(ICR) BR mice (Swiss mouse-derived outbred strain), animals were exposed to vinyl acetate (0, 50, 200, or 600 ppm) for 104 weeks. In both males and females, tracheal epithelial hyperplasia was significantly increased in the 600-ppm group and submucosal gland hyperplasia was significantly increased in the 200- and 600-ppm groups, compared to the respective controls (Bogdanffy et al. 1994a).
- In studies of male and female Swiss mice, F_0 animals were administered 0, 1000, or 5000 ppm vinyl acetate in drinking water starting from 17 weeks of age for 78 weeks. F_1 animals were exposed to 0, 1000, or 5000 ppm vinyl acetate starting *in utero* on gestation day 12, through lactation, and in drinking water *ad libitum* from weaning until 78 weeks of age (Maltoni et al. 1997). The authors reported

[24] The same finding was referred to as “basal cell activation” by the JBRC (1995) report, and “basal cell hyperplasia” in the publication by Umeda et al. (2004). JBRC (1995) considered the basal cell activation to be a growth-related cell change and a lesion that represents an early stage of cancer.

observations of increased dysplasia in various tissues of treated mice in these studies, as follows:

  - In F_0 males, a statistically significant increase in squamous cell dysplasia of the esophagus was observed at the high dose compared to controls. In F_1 males, marginal (not statistically significant) increases in squamous cell dysplasia of the tongue, esophagus, forestomach and Zymbal gland were observed at the high dose compared to controls. No dysplasia at any of these sites was observed in F_0 or F_1 controls, except for Zymbal gland.
  - In F_0 females, a statistically significant increase in squamous cell dysplasia of the esophagus was observed at the high dose compared to controls. Marginal (not statistically significant) increases in squamous cell dysplasia of the tongue and Zymbal gland were also observed in treated F_0 females. In F_1 females, statistically significant increases in squamous cell dysplasia of the tongue, esophagus, and Zymbal gland were observed at the high dose compared to controls. No dysplasia at any of these sites was observed in F_0 or F_1 controls, except for Zymbal gland.

- In studies of male and female Crj:BDF1 mice, animals were orally administered vinyl acetate (0, 400, 2000, or 10000 ppm) in drinking water for 104 weeks. Macroscopic and histopathological examinations were performed on all animals. In males, statistically significant increases in basal cell activation, squamous cell hyperplasia, and epithelial dysplasia of the oral cavity, and basal cell activation of the esophagus were observed in the 10000-ppm dose group compared to controls. In females, statistically significant increases in basal cell activation of the oral cavity, esophagus, and larynx, squamous cell hyperplasia of the oral cavity, and epithelial dysplasia of the oral cavity and esophagus were observed in the 10000-ppm dose group compared to controls (Umeda et al. 2004).

Summary

Vinyl acetate increased cellular proliferation, hyperplasia, or dysplasia in rodents. These effects were observed in both inhalation and oral exposure studies and findings were predominantly observed in the upper respiratory and digestive tracts (e.g., nose, oral cavity, esophagus, forestomach, trachea). In male rats, increased cell proliferation was observed in the nasal respiratory and olfactory epithelia after a single inhalation exposure, and in the nasal olfactory epithelium after 20 repeated exposures. Cell proliferation of the oral cavity was increased in rats and mice exposed to vinyl acetate via drinking water for 92 days. Tissue concordance between tumors and hyperplasia/dysplasia was observed for several sites in some long-term cancer bioassays of vinyl acetate. For example, in female rats, hyperplasia and tumors were observed in the nasal cavity, esophagus, and thyroid tissues. In male mice, dysplasia

and tumors were observed in the esophagus in one set of studies, while in another hyperplasia and tumors were observed in the oral cavity and esophagus. Finally, in female mice, hyperplasia and tumors were observed in the oral cavity and forestomach.

6. SIMILARITIES BETWEEN VINYL ACETATE AND ITS METABOLITE ACETALDEHYDE: CARCINOGENCIGY AND GENOTOXICITY

IARC reviewed vinyl acetate in 1995 and classified it as a Group 2B carcinogen (IARC 1995). IARC (1995)'s classification for vinyl acetate is based on the following considerations, as noted in the "Overall evaluation" section of the monograph:

> "Vinyl acetate is possibly carcinogenic to humans (Group 2B). In making the overall evaluation, the Working Group took into account the following evidence:
>
> (i) Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues.
>
> (ii) There is sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde (IARC 1987). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation.
>
> (iii) Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*."

Shared tumor sites/types and genotoxicity endpoints between vinyl acetate and acetaldehyde are provided here (Table 31).

Table 31. Summary of data on carcinogenicity and genotoxicity for vinyl acetate and acetaldehyde

Toxicity	Exposure route or specific endpoint	Vinyl Acetate [1]	Acetaldehyde [2]
Carcinogenicity	**Inhalation**	• **Nasal tumors in rats** • Laryngeal tumors in rats	• **Nasal tumors in rats** • Laryngeal tumors in hamsters
	Drinking water	• **Hemolymphoreticular cancer (leukemia and lymphoma combined) in rats** • **Pancreatic tumors (islet cell adenoma and exocrine adenoma) in rats** • **Mammary gland tumors in rats (adenocarcinoma) and mice (liposarcoma)** • Oral cavity, lip, and tongue tumors in rats and mice • Pharyngeal tumors in rats • Laryngeal tumors in mice • Esophageal tumors in rats and mice • Forestomach tumors in rats and mice • Lung tumors in mice • Liver tumors in rats • Adrenal tumors in rats • Pituitary gland tumors in rats • Thyroid tumors in rats • Uterine tumors in rats and mice • Testicular tumors in rats • Lymphoma of the spleen in mice • Zymbal gland tumors in mice	• **Hemolymphoreticular cancer (leukemia and lymphoma combined) in rats** • **Pancreatic tumors (islet-cell adenoma) in rats** • **Mammary gland tumors (benign fibroma or fibroadenoma) in rats** • Nasal cavity tumors (carcinoma) in rats • Cancer of the bone (osteosarcoma) in rats
Genotoxicity	Chromosomal effects	• Micronuclei formation in human cells *in vitro* and rodents *in vivo*	• Micronuclei formation in human and rat cells *in vitro* and mice *in vivo*

Toxicity	Exposure route or specific endpoint	Vinyl Acetate [1]	Acetaldehyde [2]
		• Chromosomal aberrations in exposed humans, human cells *in vitro,* and rodents *in vivo* • Sister chromatid exchange in human and animal cells *in vitro* and rodents *in vivo*	• Chromosomal aberrations in human and rat cells *in vitro* and rats *in vivo* • Sister chromatid exchange in human and hamster cells *in vitro* and mice *in vivo*
	DNA damage	• Formation of DNA adducts in rats *in vivo* (e.g., N2-Ethyl-dG, N2-propano-dG) • Increases in DNA-protein crosslinks in human and rodent cells *in vitro* and in an acellular system	• Formation of DNA adducts in exposed humans, human and rodent cells *in vitro*, rodents *in vivo* (e.g., N2-Ethyl-dG, N2-propano-dG) • Increases in DNA-protein crosslinks in human and rodent cells *in vitro* and in an acellular system • DNA strand breaks in human cells *in vitro*
	Mutagenicity	• Mutations at *thymidine kinase* locus in human and mouse cells *in vitro* • Did not induce mutations at *HPRT* locus in human cells *in vitro* • Did not induce mutations in *S. typhimurium* or *E. coli*	• Mutations at *thymidine kinase* locus in human and mouse cells *in vitro* • Mutations at *HPRT* locus in human cells *in vitro* • Did not induce mutations in *S. typhimurium* or *E. coli* (although positive in one *E. coli* study) • Mutations at *TP53* locus in human cells *in vitro* • Mutations in fungus

Common tumor types between vinyl acetate and acetaldehyde are shown in bold.

[1] See Sections 4 and 5.2.2 for references.

[2] See Albertini (2013) and IARC (1999) for references.

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APPENDIX A. LITERATURE SEARCH ON THE CARCINOGENICITY OF VINYL ACETATE

Literature searches on the carcinogenicity of vinyl acetate were conducted mainly in May 2023. The goal was to identify peer-reviewed journal articles, print and digital books, reports, and gray literature that potentially reported toxicological and epidemiological information on the carcinogenicity of this chemical.

As described below, we used an approach similar to that recommended by the National Toxicology Program (NTP) Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2015).

The searches were conducted using the following three approaches:

- Primary searches in major biomedical databases, conducted by OEHHA librarian Nancy Firchow, MLS.
- Searches in other data sources, including authoritative reviews and reports, and databases or web resources, conducted by OEHHA scientists and the OEHHA librarian.
- Additional focused searches, conducted by OEHHA scientists.

In addition to information identified from these searches, OEHHA also considered the following:

- Submissions received during the data call-in period (July 7 – September 18, 2023) (https://oehha.ca.gov/proposition-65/crnr/request-relevant-information-carcinogenicity-vinyl-acetate)

Primary Search Process

Data Sources

Table A1 lists the data sources that were searched to find information on vinyl acetate. The list is adapted from the recommendation by the NTP Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2015), based on availability and suitability for this topic.

Table A1. Biomedical literature databases used in primary literature search

PubMed (National Library of Medicine) (https://www.ncbi.nlm.nih.gov/pmc/)
Embase (https://www.embase.com/)
Scopus (https://www.scopus.com/)
SciFinder-n (https://scifinder-n.cas.org/)
ToxPlanet (https://chemical-search.toxplanet.com/)
Google Scholar (https://scholar.google.com/)

Search Term Identification

- The US EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) was used to identify synonyms for vinyl acetate. The PubMed MeSH database (https://www.ncbi.nlm.nih.gov/mesh/) was used to find subject headings and other index terms related to the chemical.
- The PubMed Cancer filter (https://www.nlm.nih.gov/bsd/pubmed_subsets/cancer_strategy.html) was used for cancer-related terminology.
- National Toxicology Program's Standard Search Strings for Literature Database Searches: Appendix to the Draft Handbook for Preparing Report on Carcinogens Monographs (NTP 2016) was used to identify search strategies for Human Epidemiology, Experimental Animals, Absorption, Distribution, Metabolism and Elimination (ADME), Key Characteristics of Carcinogens, and Other Mechanistic concepts.
- Additional strategies for Key Characteristics of Carcinogens were drawn from those used by IARC (Barupal et al. 2021).

Primary Search Execution

Searches were executed in PubMed, Embase, Scopus, SciFinder-N, ToxPlanet, and Google Scholar in May 2023. Eight separate searches were done in PubMed, Embase and Scopus. These searches were for:

- Human cancer studies
- Animal cancer studies
- Pharmacokinetics and metabolism (ADME) studies
- Studies on key characteristics of carcinogens and other mechanistic concepts
- Acetaldehyde metabolism
- Vinyl acetate and acetaldehyde studies
- Acetaldehyde and CYP450 or monooxygenase studies

- Enzyme polymorphisms

The basic structure used for each search is shown in Table A2 through Table A9. Detailed PubMed search strategies showing specific search terms and syntax are shown in Table A13 through Table A20.

Table A2. Search structure for human cancer studies (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Vinyl acetate terms
#2	Cancer terms (PubMed Cancer Filter)
#3	Human Epidemiological Study terms (RoC Strategy)
#4	#1 AND #2 AND #3

Table A3. Search structure for animal cancer studies (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Vinyl acetate terms
#2	Cancer terms (PubMed Cancer Filter)
#3	Experimental Animals terms (RoC Strategy)
#4	#1 AND #2 AND #3
#5	#4 NOT (drug delivery terms, copolymer terms)

Table A4. Search structure for pharmacokinetic and metabolism (ADME) studies (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Vinyl acetate terms
#2	ADME terms (RoC Strategy)
#3	#1 AND #2
#4	Drug delivery terms, copolymer terms, chemical synthesis terms
#5	#3 NOT #4

Table A5. Search structure for studies on key characteristics of carcinogens and other mechanistic concepts (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Vinyl acetate terms
#2	RoC Key Characteristics of Carcinogens strategy
#3	IARC Key Characteristics of Carcinogens strategy
#4	Other mechanistic terms (RoC strategy)
#5	#1 AND (#2 OR #3 OR #4)
#6	Drug delivery terms, copolymer terms, chemical synthesis terms
#7	#5 NOT #6

Table A6. Search structure for studies on acetaldehyde metabolism (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Acetaldehyde metabolism terms
#2	Human and animal terms
#3	Alcohol and ethanol terms
#3	(#1 AND #2) NOT #3

Table A7. Search structure for studies on vinyl acetate and acetaldehyde (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Acetaldehyde metabolism terms
#2	Human and animal terms
#3	Vinyl acetate terms
#3	#1 AND #2 AND #3

Table A8. Search structure for studies on acetaldehyde and cytochrome P450 or monooxygenase (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Acetaldehyde metabolism terms
#2	Human and animal terms
#3	Cytochrome P450 and monooxygenase terms
#3	#1 AND #2 AND #3

Table A9. Search structure for studies on enzyme polymorphisms (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	Carboxylesterase and aldehyde dehydrogenase terms
#2	Polymorphism term
#3	#1 AND #2

The searches were run first in PubMed. Then the search terms and syntax were tailored according to the search features unique to the other databases. For example, Embase uses different subject headings than PubMed, so the Emtree subject heading list was searched to identify equivalent terms to replace the MeSH terms used in the PubMed searches.

Two separate searches were run in SciFinder-N. Searches in this database were divided into Human and Animal evidence streams. The basic structure used in each search is shown in Tables A10 and A11.

Table A10. Human cancer epidemiologic studies search structure (SciFinder-N)

Search step	Search Concepts
#1	Vinyl acetate terms
#2	Limit to Journal Article
#3	Limit to human concept
#4	Limit to Database "CAplus"
#5	Search within results: epidemiology terms
#6	Search within results: cancer terms

CAplus (chemical abstract plus) is a database of chemical information that can be accessed via SciFinder-N.

Table A11. Animal studies search structure (SciFinder-N)

Search step	Search Concepts
#1	Vinyl acetate terms
#2	Limit to Journal Article
#3	Limit to animal concept
#4	Limit to Database "CAplus"
#5	EXCLUDE Database Medline

CAplus, chemical abstract plus.

Results from all databases were uploaded to EndNote, maintaining separate libraries for each of the eight concepts searched. Duplicates were removed. The results of the primary searches for vinyl acetate are shown in Table A12.

Table A12. Vinyl acetate search results

Search	PubMed Results	Embase Results	Scopus Results	SciFinder-n Results	Unique Results After Deduplication
Human cancer studies	8	20	18	13	37
Animal cancer studies	50	48	113	4	137
Pharmacokinetics and metabolism (ADME)	34	145	77	NA	196
Studies on key characteristics of carcinogens and other mechanistic concepts	74	100	75	NA	165
Acetaldehyde metabolism	599	219	856	NA	1289
Acetaldehyde and vinyl acetate	4	4	10	NA	11
Acetaldehyde and CYP450/ monooxygenase	55	77	121	NA	194
Enzyme polymorphisms	1738	1090	1854	NA	2343

NA, not applicable.

Other Data Source Searches

Several additional databases and websites of authoritative bodies were searched for data and additional references that may have been missed in the primary literature search. For example, an additional focused search was conducted in Google Scholar for human cancer studies using the search string:

> "vinyl acetate" expos (worker|workplace|"polymer production"|adhesive|paint|coating|textile|packag|emulsion|fabric) (cohort|"case control"|case|epidemiol)

Authoritative reviews and reports

- International Agency for Research on Cancer (IARC) publications, including but not limited to IARC Monographs on the Identification of Carcinogenic Hazards to Humans (https://monographs.iarc.fr/)

- NTP publications, including but not limited to, technical reports, nominations for toxicological evaluation documents, RoC monographs, RoC background documents or monographs, and other NTP reports (https://ntp.niehs.nih.gov)
- US Environmental Protection Agency (US EPA) publications (https://www.epa.gov/)
- US Food and Drug Administration (US FDA) publications (https://www.fda.gov/)
- National Institute for Occupational Safety and Health (NIOSH) publications (https://www.cdc.gov/niosh/index.htm)

Other databases and web resources

- Computational Toxicology (CompTox) Chemicals Dashboard, (https://www.epa.gov/chemical-research/comptox-chemicals-dashboard)
- Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles (https://www.atsdr.cdc.gov/toxprofiles/index.asp)
- PubChem BioAssay (National Library of Medicine) (https://www.ncbi.nlm.nih.gov/pcassay)

Additional Focused Searches

In addition to the primary searches listed above, focused searches were conducted for exposure and animal tumor pathology. Additional relevant literature was identified from citations of individual articles. Some relevant publications were also identified via updated PubMed search results after May 2023.

Introduction (Sections 1.2, 1.3, and 1.4)

Studies for the Introduction (use, exposure, and review by other agencies) were mainly identified from references cited by reviews on vinyl acetate, such as IARC (1995) or ATSDR (2023), or other reviews identified in the main search. Additional focused searches in PubMed were conducted to identify new studies published after the reviews using “vinyl acetate” AND selected keywords (e.g., “exposure”, “concentration”, “chewing gum” or “cigarette”). Per the CIC’s recommendation from the February 2024 meeting, the classification by the European Union was identified by searching the European Chemicals Agency (ECHA) website to obtain the most recent cancer classification.

Animal tumor pathology (incorporated in the Carcinogenicity Studies in Animals Section)

Focused searches were conducted using:

- Boorman's Pathology of the Rat: edited by Suttie AW, Leininger JR, and Bradley AE., 2018.
- NTP historical controls database (https://ntp.niehs.nih.gov/sites/default/files/ntp/historical_controls/nih-07_1999/r_hcrpt_rte19991223.rpt), and searching for information specific to tumor site/type.
- Charles River Laboratories historical controls database by Charles River Laboratories (http://www.centerforfoodsafety.org/files/charles-river-2004_39868.pdf)

Additional relevant literature was identified from citations in individual book chapters or articles.

Literature Screen Processes

Use of Health Assessment Workspace Collaborative (HAWC)

HAWC (https://hawcproject.org/about/) was used as a tool to screen and tag the literature on the carcinogenicity of vinyl acetate, following the guidance provided in the NTP RoC Handbook (NTP 2015).

Importing the EndNote libraries into HAWC

Citations retrieved from the literature searches for human cancer studies, animal cancer studies, and studies on key characteristics of carcinogens and other mechanistic concepts and citations retrieved from the SWIFT AS screening projects for studies related to pharmacokinetics and metabolism were uploaded to EndNote libraries, and duplicates were removed. Next, these EndNote libraries were uploaded to HAWC for multi-level screening using specific inclusion and exclusion criteria.

Screening and tagging references

In Level 1 screening, each citation was first screened by at least one OEHHA scientist, based solely on titles and abstracts, to eliminate studies or articles that do not contain information on vinyl acetate on any of the key topics covered in this cancer hazard identification document, such as cancer studies in humans and animals, toxicokinetics, metabolism, genotoxicity, or other cancer-associated mechanisms. The level 1 screen was intended to identify all studies deemed to have a reasonable possibility of containing information that could be useful for the review process. Papers identified for

inclusion during Level 1 screening were tagged in HAWC according to key topics. A paper can be assigned (or tagged) to one or more of the key topic(s). A positive response by only one of the reviewers was sufficient to pass a publication on to the next review level.

In Level 2 screening, the full papers were obtained for all citations that passed the Level 1 screen. These full papers were screened independently by at least one OEHHA scientist, using similar inclusion/exclusion criteria as was used in the Level 1 screening. However, Level 2 reviewers could make more accurate judgments about the relevance of the citations because they were reviewing the full text of the articles, in addition to the title and abstract.

Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC. Level 1 and 2 screenings were conducted and HAWC search results were updated if additional relevant studies in addition to those cited in the original set of publications ("secondary citations") were identified.

See Figure A1 for the overview of the HAWC literature screening results (literature tag tree) for the vinyl acetate HAWC project.

Use of SWIFT (Sciome Workbench for Interactive Computer-Facilitated Text-mining) Active Screener (SWIFT AS)

For pharmacokinetics and metabolism-related topics identified from the primary searches (Table A12), SWIFT AS (Howard et al. 2020), which incorporates machine learning (i.e., artificial intelligence), was used as a tool to facilitate the initial screening of references from the primary searches. Five distinct Endnote libraries were created and three were screened by SWIFT AS:[25]

- A project that included all search results for vinyl acetate "pharmacokinetic and metabolism (ADME) studies" (196 references)
- A project that included all search results for "acetaldehyde metabolism studies" (1289 references)
- A project that included all search results for "enzyme polymorphisms" for vinyl acetate (2343 references)
- A project that included all search results for "acetaldehyde and vinyl acetate studies" (11 references; SWIFT AS not used)
- A project that included all search results for "acetaldehyde and CYP450 or monooxygenase studies" (194 references; SWIFT AS not used)

[25] The numbers of references shown below for each project do not include the full sets of references selected and used as 'training seeds' in developing the project-specific AI models for screening in SWIFT AS.

The screening of the three SWIFT AS projects was completed between June 2023 and July 2023 (https://www.sciome.com/swift-activescreener/). In each of the projects, two OEHHA scientists independently completed the screening for a decision to be made on each title and abstract, following predefined inclusion and exclusion criteria. This initial screening in SWIFT AS allowed for efficient initial literature inclusion and exclusion with the help of artificial intelligence.

Use of Table Builder in the organization of epidemiologic data

Table Builder (Shapiro et al. 2018), a web-based application, was applied to systematically extract and analyze the data that were included in Section 3, Carcinogenicity studies in humans. Table Builder was also used as a custom-made database to generate Word tables in this document.

Summary

More than 1785 references, including peer-reviewed journal articles and government reports, were identified for inclusion through these search strategies. Among these, over 170 references were cited in this document. See Figure A1 for the HAWC literature screening results.

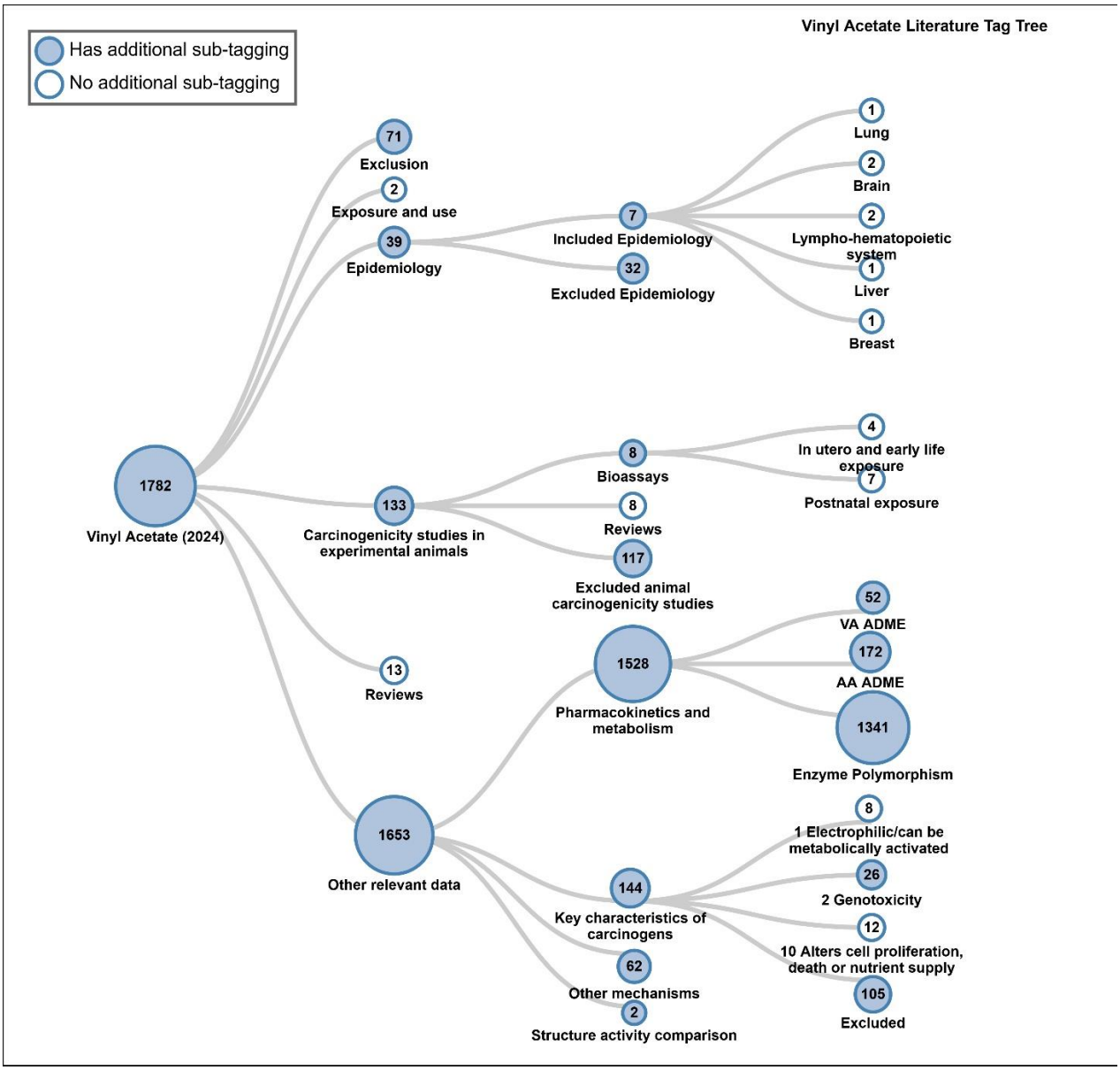

Figure A1. Overview of HAWC literature screening results for vinyl acetate.
The number of publications is indicated in each node of the literature tag tree.

Detailed PubMed Literature Search Strategies – Primary Searches

Table A13. PubMed search strategy for Human Cancer Studies

Set	Search Terms	Retrieval	Concept Group
1	"vinyl acetate"[nm] OR "vinyl acetate"[tiab] OR 108-05-4[rn] OR "acetic acid ethenyl ester"[tiab] OR "ethylene acetate"[tiab:~0] OR vinyl acetate[tiab]	2495	chemical terms
2	neoplasms OR American Cancer Society OR angiogenesis inducing agents OR antibodies, neoplasm OR antigens, neoplasm OR antineoplastic agents OR antineoplastic protocols OR biomarkers, tumor OR biopsy [mh] OR biopsy [tw] OR bone marrow purging OR bone marrow transplantation OR cancer care facilities OR cancer vaccines OR carcinogenicity tests OR carcinogens OR chemoembolization, therapeutic OR clonal evolution [mh] OR clonal evolution [tw] OR colonography, computed tomographic OR colonoscopy OR colposcopy OR combined modality therapy OR cryosurgery OR cytapheresis OR dna, neoplasm OR drug resistance, neoplasm OR drug screening assays, antitumor OR early detection of cancer OR gene expression regulation, neoplastic OR genes, neoplasm OR graft vs tumor effect OR hematopoietic stem cell transplantation OR hematopoietic stem cell mobilization OR immunotherapy, adoptive OR leukostasis OR lymph node excision OR lymphocytes, tumor-infiltrating OR mammography OR mastectomy OR medical oncology OR metastasectomy OR mohs surgery OR myelodysplastic-myeloproliferative diseases OR neoplasm grading OR neoplasm proteins OR neoplasm staging OR neoplasm transplantation OR neoplastic processes OR neoplastic stem cells OR oncogene fusion OR oncogenic viruses OR oncology nursing OR oncology service, hospital OR oncolytic viruses OR papanicolaou test [mh] OR papillomavirus vaccines OR peripheral blood stem cell transplantation OR polyomavirus OR radiotherapy OR radiotherapy planning, computer assisted OR rna, neoplasm OR second-look surgery OR SEER program OR stem cell transplantation [mh:noexp] OR transplantation conditioning OR tumor cells, cultured OR tumor escape OR tumor lysis syndrome OR tumor necrosis factors OR receptors, tumor necrosis factor OR tumor necrosis factor receptor-associated peptides and proteins OR ultrasonography, mammary OR AACR OR AJCC [tw] OR (ASCO NOT fungi) OR IARC OR "National Cancer Institute (U.S.)" [mh] OR UICC OR aCML [tw] OR AGCUS [tw] OR AILD [tw] OR AML [tw] OR ANLL [tw] OR ASCUS [tw] OR ATLL [tw] OR BRCA [tw] OR BRCA1 [tw] OR BRCA2 [tw] OR CIN [tw] OR CLL [tw] OR CMML [tw] OR CMPD [tw] OR ECCL [tw] OR EGIST [tw] OR FMTC [tw] OR GLNH [tw] OR HNPCC [tw] OR HNSCC [tw] OR HPV [tw] OR HSIL [tw] OR ICD O [tw] OR JCML [tw] OR JMML [tw] OR LGLL [tw] OR MGUS [tw] OR MLH1[tw] OR MPD [tw] OR MSH2[tw] OR NSCLC [tw] OR RAEB [tw] OR RCMD [tw] OR SCLC [tw] OR VOD [tw] OR 5q syndrome [tw] OR BCR ABL [tw] OR c erbB 2 [tw] OR c erbB2 [tw] OR carney complex [tw] OR cone biopsy [tw] OR denys drash [tw] OR essential thrombocythemia [tw] OR estrogen receptor negative [tw] OR estrogen receptor positive [tw] OR li fraumeni [tw] OR meigs syndrome [tw] OR molar pregnancy [tw] OR mycosis fungoides [tw] OR peutz jeghers [tw] OR sentinel lymph node [tw] OR sezary syndrome [tw] OR struma ovarii [tw] OR sturge weber [tw] OR zollinger ellison [tw] OR (aberrant [tw] AND crypt [tw] AND foci [tw]) OR ((anti-n-methyl-d-aspartate [tw] OR anti-nmda) AND encephalitis [tw]) OR (barrett [tw] AND esophagus [tw]) OR (gestational [tw] AND trophoblastic [tw]) OR (microsatellite [tw] AND instability [tw]) OR (paget [tw] AND (breast [tw] OR nipple [tw])) OR (polycythemia [tw] AND vera [tw]) OR (radiation [tw] AND therapy [tw]) OR (WAGR [tw] AND	7356145	PubMed Cancer terms

Set	Search Terms	Retrieval	Concept Group
	syndrome [tw]) OR (pap [tw] AND (smear [tw] OR smears [tw])) OR cervical smear [tw] OR cervical smears [tw] OR pap test [tw] OR pap tests [tw] OR (PSA [tw] AND prostate) OR PSA test [tw] OR PSA testing [tw] OR (prostate [tw] AND specific [tw] AND antigen [tw]) OR acanthoma [tw] OR acanthomas [tw] OR acrochordon [tw] OR acrochordons [tw] OR acrospiroma [tw] OR acrospiromas [tw] OR adamantinoma [tw] OR adamantinomas [tw] OR adenoacanthoma [tw] OR adenoacanthomas [tw] OR adenoameloblastoma [tw] OR adenoameloblastomas [tw] OR adenocanthoma [tw] OR adenocanthomas [tw] OR adenocarcinoma [tw] OR adenocarcinomas [tw] OR adenofibroma [tw] OR adenofibromas [tw] OR adenolipoma [tw] OR adenolipomas [tw] OR adenolymphoma [tw] OR adenolymphomas [tw] OR adenoma [tw] OR adenomas [tw] OR adenomatosis [tw] OR adenomatous [tw] OR adenomyoepithelioma [tw] OR adenomyoepitheliomas [tw] OR adenomyoma [tw] OR adenomyomas [tw] OR adenosarcoma [tw] OR adenosarcomas [tw] OR adenosis [tw] OR aesthesioneuroblastoma [tw] OR aesthesioneuroblastomas [tw] OR ameloblastoma [tw] OR ameloblastomas [tw] OR amyloidoses [tw] OR amyloidosis [tw] OR anaplasia [tw] OR androblastoma [tw] OR androblastomas [tw] OR angioblastoma [tw] OR angioblastomas [tw] OR angioendothelioma [tw] OR angioendotheliomas [tw] OR angioendotheliomatosis [tw] OR angiofibroma [tw] OR angiofibromas [tw] OR angiofibrosarcoma [tw] OR angiogenesis factor [tw] OR angiokeratoma [tw] OR angiokeratomas [tw] OR angioleiomyoma [tw] OR angioleiomyomas [tw] OR angiolipoma [tw] OR angiolipomas [tw] OR angioma [tw] OR angiomas [tw] OR angiomatosis [tw] OR angiomyolipoma [tw] OR angiomyolipomas [tw] OR angiomyoma [tw] OR angiomyomas [tw] OR angiomyxoma [tw] OR angiomyxomas [tw] OR angioreticuloma [tw] OR angioreticulomas [tw] OR angiosarcoma [tw] OR angiosarcomas [tw] OR anticancer [tw] OR anticarcinogenesis [tw] OR anticarcinogenic [tw] OR antimutagenesis [tw] OR antineoplastic [tw] OR antioncogene [tw] OR antioncogenes [tw] OR antitumor [tw] OR antitumors [tw] OR antitumour [tw] OR antitumours [tw] OR apudoma [tw] OR apudomas [tw] OR argentaffinoma [tw] OR argentaffinomas [tw] OR arrhenoblastoma [tw] OR arrhenoblastomas [tw] OR astroblastoma [tw] OR astroblastomas [tw] OR astrocytoma [tw] OR astrocytomas [tw] OR astroglioma [tw] OR astrogliomas [tw] OR atypia [tw] OR baltoma [tw] OR basiloma [tw] OR basilomas [tw] OR biochemotherapies [tw] OR biochemotherapy [tw] OR bioradiotherapy [tw] OR Birt-Hogg-Dube [tw] OR blastoma [tw] OR blastomas [tw] OR Buschke-Lowenstein [tw] OR cachexia [tw] OR cancer [tw] OR cancerous [tw] OR cancers [tw] OR carcinogen [tw] OR carcinogenesis [tw] OR carcinogenic [tw] OR carcinogens [tw] OR carcinoid [tw] OR carcinoma [tw] OR carcinomas [tw] OR carcinomatosis [tw] OR carcinosarcoma [tw] OR carcinosarcomas [tw] OR cavernoma [tw] OR cavernomas [tw] OR cementoma [tw] OR cementomas [tw] OR cerbB2 [tw] OR ceruminoma [tw] OR ceruminomas [tw] OR chemodectoma [tw] OR chemodectomas [tw] OR chemoimmunoradiotherapy [tw] OR chemoimmunotherapies [tw] OR chemoimmunotherapy [tw] OR chemoprevention [tw] OR chemoradiation [tw] OR chemoradiotherapies [tw] OR chemoradiotherapy [tw] OR cherubism [tw] OR chloroma [tw] OR chloromas [tw] OR cholangiocarcinoma [tw] OR cholangiocarcinomas [tw] OR cholangiohepatoma [tw] OR cholangioma [tw] OR cholangiomas [tw] OR cholangiosarcoma [tw] OR cholesteatoma [tw] OR cholesteatomas [tw] OR chondroblastoma [tw] OR chondroblastomas [tw] OR chondroma [tw] OR chondromas [tw] OR chondrosarcoma [tw] OR chondrosarcomas [tw]		

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	OR chordoma [tw] OR chordomas [tw] OR chorioadenoma [tw] OR chorioadenomas [tw] OR chorioangioma [tw] OR chorioangiomas [tw] OR choriocarcinoma [tw] OR choriocarcinomas [tw] OR chorioepithelioma [tw] OR chorioepitheliomas [tw] OR chorionepithelioma [tw] OR chorionepitheliomas [tw] OR choristoma [tw] OR choristomas [tw] OR chromaffinoma [tw] OR chromaffinomas [tw] OR cocarcinogenesis [tw] OR collagenoma [tw] OR collagenomas [tw] OR colonoscopies [tw] OR coloscopy [tw] OR coloscopies [tw] OR comedocarcinoma [tw] OR comedocarcinomas [tw] OR condyloma [tw] OR condylomas [tw] OR corticotropinoma [tw] OR corticotropinomas [tw] OR craniopharyngioma [tw] OR craniopharyngiomas [tw] OR cylindroma [tw] OR cylindromas [tw] OR cyst [tw] OR cysts [tw] OR cystadenocarcinoma [tw] OR cystadenocarcinomas [tw] OR cystadenofibroma [tw] OR cystadenofibromas [tw] OR cystadenoma [tw] OR cystadenomas [tw] OR cystoma [tw] OR cystomas [tw] OR cystosarcoma [tw] OR cystosarcomas [tw] OR dentinoma [tw] OR dentinomas [tw] OR dermatofibroma [tw] OR dermatofibromas [tw] OR dermatofibrosarcoma [tw] OR dermatofibrosarcomas [tw] OR dermoid [tw] OR desmoid [tw] OR desmoplastic [tw] OR dictyoma [tw] OR dysgerminoma [tw] OR dysgerminomas [tw] OR dyskeratoma [tw] OR dyskeratomas [tw] OR dysmyelopoiesis [tw] OR dysplasia [tw] OR dysplastic [tw] OR ectomesenchymoma [tw] OR ectomesenchymomas [tw] OR elastofibroma [tw] OR elastofibromas [tw] OR enchondroma [tw] OR enchondromas [tw] OR enchondromatosis [tw] OR endothelioma [tw] OR endotheliomas [tw] OR ependymoblastoma [tw] OR ependymoblastomas [tw] OR ependymoma [tw] OR ependymomas [tw] OR epidermoid [tw] OR epithelioma [tw] OR epitheliomas [tw] OR erythroleukaemia [tw] OR erythroleukaemias [tw] OR erythroleukemia [tw] OR erythroleukemias [tw] OR erythroplakia [tw] OR erythroplakias [tw] OR erythroplasia [tw] OR esthesioneuroblastoma [tw] OR esthesioneuroblastomas [tw] OR esthesioneuroepithelioma [tw] OR esthesioneuroepitheliomas [tw] OR exostosis [tw] OR fibroadenoma [tw] OR fibroadenomas [tw] OR fibroadenosarcoma [tw] OR fibroadenosis [tw] OR fibrochondrosarcoma [tw] OR fibroelastoma [tw] OR fibroelastomas [tw] OR fibroepithelioma [tw] OR fibroepitheliomas [tw] OR fibrofolliculoma [tw] OR fibrofolliculomas [tw] OR fibroid [tw] OR fibroids [tw] OR fibrolipoma [tw] OR fibrolipomas [tw] OR fibroliposarcoma [tw] OR fibroma [tw] OR fibromas [tw] OR fibromatosis [tw] OR fibromyoma [tw] OR fibromyomas [tw] OR fibromyxolipoma [tw] OR fibromyxoma [tw] OR fibromyxomas [tw] OR fibroodontoma [tw] OR fibroodontomas [tw] OR fibrosarcoma [tw] OR fibrosarcomas [tw] OR fibrothecoma [tw] OR fibrothecomas [tw] OR fibroxanthoma [tw] OR fibroxanthomas [tw] OR fibroxanthosarcoma [tw] OR fibroxanthosarcomas [tw] OR ganglioblastoma [tw] OR ganglioblastomas [tw] OR gangliocytoma [tw] OR gangliocytomas [tw] OR ganglioglioma [tw] OR gangliogliomas [tw] OR ganglioneuroblastoma [tw] OR ganglioneuroblastomas [tw] OR ganglioneurofibroma [tw] OR ganglioneurofibromas [tw] OR ganglioneuroma [tw] OR ganglioneuromas [tw] OR gastrinoma [tw] OR gastrinomas [tw] OR germinoma [tw] OR germinomas [tw] OR glioblastoma [tw] OR glioblastomas [tw] OR gliofibroma [tw] OR gliofibromas [tw] OR glioma [tw] OR gliomas [tw] OR gliomatosis [tw] OR glioneuroma [tw] OR glioneuromas [tw] OR gliosarcoma [tw] OR gliosarcomas [tw] OR glomangioma [tw] OR glomangiomas [tw] OR glomangiomatosis [tw] OR glomangiomyoma [tw] OR glomangiomyomas [tw] OR glomangiosarcoma [tw] OR glomangiosarcomas [tw] OR glucagonoma [tw] OR glucagonomas		

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	meningiomas [tw] OR meningiomatosis [tw] OR mesenchymoma [tw] OR mesenchymomas [tw] OR mesonephroma [tw] OR mesonephromas [tw] OR mesothelioma [tw] OR mesotheliomas [tw] OR metaplasia [tw] OR metastases [tw] OR metastasis [tw] OR metastatic [tw] OR microcarcinoma [tw] OR microcarcinomas [tw] OR microglioma [tw] OR microgliomas [tw] OR micrometastases [tw] OR micrometastasis [tw] OR mucositis [tw] OR myelodysplasia [tw] OR myelodysplasias [tw] OR myelodysplastic [tw] OR myelofibrosis [tw] OR myelolipoma [tw] OR myelolipomas [tw] OR myeloma [tw] OR myelomas [tw] OR myelomatosis [tw] OR myeloproliferation [tw] OR myeloproliferations [tw] OR myeloproliferative [tw] OR myelosuppression [tw] OR myoblastoma [tw] OR myoblastomas [tw] OR myoepithelioma [tw] OR myoepitheliomas [tw] OR myofibroblastoma [tw] OR myofibroblastomas [tw] OR myofibroma [tw] OR myofibromas [tw] OR myofibromatosis [tw] OR myofibrosarcoma [tw] OR myofibrosarcomas [tw] OR myolipoma [tw] OR myolipomas [tw] OR myoma [tw] OR myomas [tw] OR myopericytoma [tw] OR myosarcoma [tw] OR myosarcomas [tw] OR myxofibroma [tw] OR myxofibromas [tw] OR myxolipoma [tw] OR myxolipomas [tw] OR myxoliposarcoma [tw] OR myxoma [tw] OR myxomas [tw] OR naevus [tw] OR neoplasia [tw] OR neoplasia [tw] OR neoplasm [tw] OR neoplasms [tw] OR neoplastic [tw] OR nephroblastoma [tw] OR nephroblastomas [tw] OR neurilemmoma [tw] OR neurilemmomas [tw] OR neurilemmomatosis [tw] OR neurilemoma [tw] OR neurilemomas [tw] OR neurinoma [tw] OR neurinomas [tw] OR neuroblastoma [tw] OR neuroblastomas [tw] OR neurocytoma [tw] OR neurocytomas [tw] OR neuroepithelioma [tw] OR neuroepitheliomas [tw] OR neurofibroma [tw] OR neurofibromas [tw] OR neurofibromatosis [tw] OR neurofibrosarcoma [tw] OR neurofibrosarcomas [tw] OR neurolipocytoma [tw] OR neuroma [tw] OR neuromas [tw] OR neuronevus [tw] OR neurothekeoma [tw] OR neurothekeomas [tw] OR nevus [tw] OR nonhodgkin [tw] OR nonhodgkins [tw] OR nonseminoma [tw] OR nonseminomas [tw] OR nonseminomatous [tw] OR odontoameloblastoma [tw] OR odontoma [tw] OR oligoastrocytoma [tw] OR oligoastrocytomas [tw] OR oligodendroglioma [tw] OR oligodendrogliomas [tw] OR oncocytoma [tw] OR oncocytomas [tw] OR oncogen [tw] OR oncogene [tw] OR oncogenes [tw] OR oncogenesis [tw] OR oncogenic [tw] OR oncogens [tw] OR oncologic [tw] OR oncologist [tw] OR oncologists [tw] OR oncology [tw] OR oncoprotein [tw] OR oncoproteins [tw] OR opsoclonus-myoclonus [tw] OR orchioblastoma [tw] OR orchioblastomas [tw] OR osteoblastoma [tw] OR osteoblastomas [tw] OR osteochondroma [tw] OR osteochondromas [tw] OR osteochondrosarcoma [tw] OR osteochondrosarcomas [tw] OR osteoclastoma [tw] OR osteoclastomas [tw] OR osteofibrosarcoma [tw] OR osteoma [tw] OR osteomas [tw] OR osteosarcoma [tw] OR osteosarcomas [tw] OR pancreatoblastoma [tw] OR pancreatoblastomas [tw] OR papilloma [tw] OR papillomas [tw] OR papillomata [tw] OR papillomatosis [tw] OR papillomavirus [tw] OR papillomaviruses [tw] OR parachordoma [tw] OR parachordomas [tw] OR paraganglioma [tw] OR paragangliomas [tw] OR paraneoplastic [tw] OR perineurioma [tw] OR perineuriomas [tw] OR phaeochromocytoma [tw] OR phaeochromocytomas [tw] OR pheochromoblastoma [tw] OR pheochromoblastomas [tw] OR pheochromocytoma [tw] OR pheochromocytomas [tw] OR pilomatricoma [tw] OR pilomatricomas [tw] OR pilomatrixoma [tw] OR pilomatrixomas [tw] OR pinealblastoma [tw] OR pinealoblastoma [tw] OR pinealoblastomas [tw] OR pinealoma [tw] OR pinealomas [tw] OR pineoblastoma [tw] OR pineoblastomas [tw] OR pineocytoma [tw] OR pineocytomas [tw] OR		

Set	Search Terms	Retrieval	Concept Group
	plasmacytoma [tw] OR plasmacytomas [tw] OR pneumoblastoma [tw] OR pneumoblastomas [tw] OR pneumocytoma [tw] OR polyembryoma [tw] OR polyembryomas [tw] OR polyhistioma [tw] OR polyhistiomas [tw] OR polyp [tw] OR polyposis [tw] OR polyps [tw] OR porocarcinoma [tw] OR porocarcinomas [tw] OR poroma [tw] OR poromas [tw] OR precancer [tw] OR precancerous [tw] OR preleukaemia [tw] OR preleukaemias [tw] OR preleukemia [tw] OR preleukemias [tw] OR premalignant [tw] OR preneoplastic [tw] OR prolactinoma [tw] OR prolactinomas [tw] OR protooncogene [tw] OR protooncogenes [tw] OR pseudotumor [tw] OR pseudotumors [tw] OR radiochemotherapy [tw] OR radioimmunotherapies [tw] OR radioimmunotherapy [tw] OR reninoma [tw] OR reninomas [tw] OR reticuloendothelioma [tw] OR reticuloendotheliomas [tw] OR reticulohistiocytoma [tw] OR reticulohistiocytomas [tw] OR reticulosis [tw] OR retinoblastoma [tw] OR retinoblastomas [tw] OR rhabdomyoma [tw] OR rhabdomyomas [tw] OR rhabdomyosarcoma [tw] OR rhabdomyosarcomas [tw] OR rhabdosarcoma [tw] OR rhabdosarcomas [tw] OR sarcoma [tw] OR sarcomas [tw] OR sarcomatosis [tw] OR schwannoma [tw] OR schwannomas [tw] OR schwannomatosis [tw] OR seminoma [tw] OR seminomas [tw] OR seminomatous [tw] OR somatostatinoma [tw] OR somatostatinomas [tw] OR somatotropinoma [tw] OR somatotropinomas [tw] OR spermatocytoma [tw] OR spiradenoma [tw] OR spiradenomas [tw] OR spongioblastoma [tw] OR spongioblastomas [tw] OR steatocystoma [tw] OR steatocystomas [tw] OR subependymoma [tw] OR subependymomas [tw] OR syringadenoma [tw] OR syringadenomas [tw] OR syringocystadenoma [tw] OR syringocystadenomas [tw] OR syringoma [tw] OR syringomas [tw] OR teratocarcinoma [tw] OR teratocarcinomas [tw] OR teratoma [tw] OR teratomas [tw] OR thecoma [tw] OR thecomas [tw] OR thymolipoma [tw] OR thymolipomas [tw] OR thymoma [tw] OR thymomas [tw] OR trichilemmoma [tw] OR trichilemmomas [tw] OR trichoadenoma [tw] OR trichoblastoma [tw] OR trichoblastomas [tw] OR trichodiscoma [tw] OR trichodiscomas [tw] OR trichoepithelioma [tw] OR trichoepitheliomas [tw] OR trichofolliculoma [tw] OR trichofolliculomas [tw] OR tricholemmoma [tw] OR tricholemmomas [tw] OR tumor [tw] OR tumorgenesis [tw] OR tumorgenic [tw] OR tumorigenesis [tw] OR tumorigenic [tw] OR tumorogenesis [tw] OR tumorogenic [tw] OR tumors [tw] OR tumour [tw] OR tumours [tw] OR vipoma [tw] OR vipomas [tw] OR waldenstrom [tw] OR waldenstroms [tw] OR xanthoastrocytoma [tw] OR xanthoastrocytomas [tw] OR xanthofibroma [tw] OR xanthofibromas [tw] OR xanthogranuloma [tw] OR xanthogranulomas [tw] OR xanthoma [tw] OR xanthomas [tw] OR xanthosarcoma [tw] OR xanthosarcomas [tw] OR Acta Oncol [ta] OR Acta Radiol Oncol Radiat Phys Biol [ta] OR Acta Radiol Oncol [ta] OR Adv Cancer Res [ta] OR Adv Immun Cancer Ther [ta] OR Ai Zheng [ta] OR Am J Cancer [ta] OR Am J Clin Oncol [ta] OR Am Soc Clin Oncol Educ Book [ta] OR Anal Cell Pathol [ta] OR Ann Oncol [ta] OR Ann Surg Oncol [ta] OR Anti cancer Drugs [ta] OR Anticancer Agents Med Chem [ta] OR Anticancer Drug Des [ta] OR Anticancer Res [ta] OR Asia Pac J Clin Oncol [ta] OR BMC Cancer [ta] OR Baillieres Clin Oncol [ta] OR Biochim Biophys Acta [ta] OR Blood Cancer J [ta] OR Br J Cancer Suppl [ta] OR Br J Cancer [ta] OR Brain Tumor Pathol [ta] OR Breast Cancer Res Treat [ta] OR Breast Cancer Res [ta] OR Breast Cancer [ta] OR Breast J [ta] OR Bull Assoc Fr Etud Cancer [ta] OR Bull Cancer Radiother [ta] OR Bull Cancer [ta] OR CA Cancer J Clin [ta] OR Can J Oncol [ta] OR Can Oncol Nurs J [ta] OR Cancer Biochem Biophys [ta] OR Cancer Biol Ther [ta] OR Cancer Biomark [ta] OR Cancer Biother Radiopharm [ta] OR		

Set	Search Terms	Retrieval	Concept Group
	Cancer Biother [ta] OR Cancer Bull [ta] OR Cancer Causes Control [ta] OR Cancer Cell Int [ta] OR Cancer Cell [ta] OR Cancer Cells [ta] OR Cancer Chemother Biol Response Modif [ta] OR Cancer Chemother Pharmacol [ta] OR Cancer Chemother Rep 2 [ta] OR Cancer Chemother Rep 3 [ta] OR Cancer Chemother Rep [ta] OR Cancer Clin Trials [ta] OR Cancer Commun [ta] OR "Cancer Commun (Lond)" [ta] OR Cancer Control [ta] OR Cancer Cytol [ta] OR Cancer Cytopathol [ta] OR Cancer Detect Prev Suppl [ta] OR Cancer Detect Prev [ta] OR Cancer Discov [ta] OR Cancer Drug Deliv [ta] OR Cancer Epidemiol Biomarkers Prev [ta] OR Cancer Epidemiol [ta] OR Cancer Gene Ther [ta] OR Cancer Genet [ta] OR Cancer Genet Cytogenet [ta] OR Cancer Genomics Proteomics [ta] OR Cancer Imaging [ta] OR Cancer Immun [ta] OR Cancer Immunol Immunother [ta] OR Cancer Immunol Res [ta] OR Cancer Inform [ta] OR Cancer Invest [ta] OR Cancer J Sci Am [ta] OR Cancer J [ta] OR Cancer Lett [ta] OR Cancer Med [ta] OR Cancer Metastasis Rev [ta] OR Cancer Microenviron [ta] OR Cancer Nurs [ta] OR Cancer Pract [ta] OR Cancer Prev Control [ta] OR Cancer Prev Res Phila [ta] OR Cancer Radiother [ta] OR Cancer Res Treat [ta] OR Cancer Res [ta] OR Cancer Sci [ta] OR Cancer Surv [ta] OR Cancer Treat Rep [ta] OR Cancer Treat Res [ta] OR Cancer Treat Res Commun [ta] OR Cancer Treat Rev [ta] OR Cancer [ta] OR Carcinogenesis [ta] OR Cell Growth Differ [ta] OR Cell Oncol Dordr [ta] OR Chin Clin Oncol [ta] OR Chin J Cancer [ta] OR Chin J Cancer [ta] OR Clin Breast Cancer [ta] OR Clin Cancer Res [ta] OR Clin Colorectal Cancer [ta] OR Clin Exp Metastasis [ta] OR Clin J Oncol Nurs [ta] OR Clin Lymphoma Myeloma Leuk [ta] OR Clin Lymphoma [ta] OR Clin Oncol R Coll Radiol [ta] OR Clin Oncol [ta] OR Clin Transl Oncol [ta] OR CNS Oncol [ta] OR Contemp Oncol [ta] OR Crit Rev Oncog [ta] OR Crit Rev Oncol Hematol [ta] OR Curr Cancer Drug Targets [ta] OR Curr Oncol Rep [ta] OR Curr Oncol [ta] OR Curr Opin Oncol [ta] OR Curr Probl Cancer [ta] OR Curr Treat Options Oncol [ta] OR Dimens Oncol Nurs [ta] OR Drug Resist Updat [ta] OR Eksp Onkol [ta] OR Endocr Relat Cancer [ta] OR Eur J Cancer B Oral Oncol [ta] OR Eur J Cancer Care Engl [ta] OR Eur J Cancer Clin Oncol [ta] OR Eur J Cancer Prev [ta] OR Eur J Cancer [ta] OR Eur J Gynaecol Oncol [ta] OR Eur J Surg Oncol [ta] OR Front Radiat Ther Oncol [ta] OR Future Oncol [ta] OR Gan No Rinsho [ta] OR Gan To Kagaku Ryoho [ta] OR Gastric Cancer [ta] OR Gastrointest Cancer Res [ta] OR Genes Chromosomes Cancer [ta] OR Gulf J Oncolog [ta] OR Gynecol Oncol [ta] OR Head Neck Oncol [ta] OR Hematol Oncol Clin North Am [ta] OR Hematol Oncol Stem Cell Ther [ta] OR Hematol Oncol [ta] OR Hered Cancer Clin Pract [ta] OR Horm Cancer [ta] OR IARC Monogr Eval Carcinog Risk Chem Hum Suppl [ta] OR IARC Monogr Eval Carcinog Risk Chem Hum [ta] OR IARC Monogr Eval Carcinog Risk Chem Man [ta] OR IARC Monogr Eval Carcinog Risks Hum Suppl [ta] OR IARC Monogr Eval Carcinog Risks Hum [ta] OR IARC Sci Publ [ta] OR Important Adv Oncol [ta] OR Indian J Cancer [ta] OR Infect Agent Cancer [ta] OR Innov Oncol Nurs [ta] OR Int Adv Surg Oncol [ta] OR Int J Biol Markers [ta] OR Int J Cancer Suppl [ta] OR Int J Cancer [ta] OR Int J Clin Oncol [ta] OR Int J Gastrointest Cancer [ta] OR Int J Gynecol Cancer [ta] OR Int J Hyperthermia [ta] OR Int J Oncol [ta] OR Int J Radiat Oncol Biol Phys [ta] OR Int J Surg Oncol [ta] OR Integr Cancer Ther [ta] OR Invasion Metastasis [ta] OR Invest New Drugs [ta] OR J Adolesc Young Adult Oncol [ta] OR J Assoc Pediatr Oncol Nurses [ta] OR J Cancer Educ [ta] OR J Cancer Epidemiol Prev [ta] OR J Cancer Res Clin Oncol [ta] OR J Cancer Res [ta] OR J Cancer Surviv [ta] OR J Chemother [ta] OR J Clin Oncol [ta]		

Set	Search Terms	Retrieval	Concept Group
	OR J Community Support Oncol [ta] OR J Dermatol Surg Oncol [ta] OR J Egypt Natl Canc Inst [ta] OR J Environ Pathol Toxicol Oncol [ta] OR J Exp Clin Cancer Res [ta] OR J Exp Ther Oncol [ta] OR J Geriatr Oncol [ta] OR J Gynecol Oncol [ta] OR J Hematol Oncol [ta] OR J Immunother Emphasis Tumor Immunol [ta] OR J Immunother [ta] OR J Mammary Gland Biol Neoplasia [ta] OR J Med Imaging Radiat Oncol [ta] OR J Natl Cancer Inst Monogr [ta] OR J Natl Cancer Inst [ta] OR J Natl Compr Canc Netw [ta] OR J Neurooncol [ta] OR J Oncol Manag [ta] OR J Oncol Pract [ta] OR J Oncol [ta] OR J Pediatr Hematol Oncol [ta] OR J Pediatr Oncol Nurs [ta] OR J Soc Integr Oncol [ta] OR J Support Oncol [ta] OR J Surg Oncol Suppl [ta] OR J Surg Oncol [ta] OR J Thorac Oncol [ta] OR Jaarb Kankeronderz Kankerbestrijd Ned [ta] OR JAMA Oncol [ta] OR JCO Clin Cancer Inform [ta] OR Jpn J Cancer Res [ta] OR Jpn J Clin Oncol [ta] OR Klin Onkol [ta] OR Lancet Oncol [ta] OR Leuk Lymphoma [ta] OR Leuk Res [ta] OR Leukemia [ta] OR Lung Cancer [ta] OR Lutte Cancer [ta] OR Magy Onkol [ta] OR Med Oncol Tumor Pharmacother [ta] OR Med Oncol [ta] OR Med Pediatr Oncol Suppl [ta] OR Med Pediatr Oncol [ta] OR Melanoma Res [ta] OR Mol Cancer Res [ta] OR Mol Cancer Ther [ta] OR Mol Cancer [ta] OR Mol Oncol [ta] OR Monogr Neoplast Dis Var Sites [ta] OR NCI Monogr [ta] OR Nat Rev Cancer [ta] OR Nat Rev Clin Oncol [ta] OR Natl Cancer Inst Monogr [ta] OR Natl Cancer Inst Res Rep [ta] OR Neoplasia [ta] OR Neoplasma [ta] OR Neuro oncol [ta] OR Nippon Gan Chiryo Gakkai Shi [ta] OR Noshuyo Byori [ta] OR Nutr Cancer [ta] OR ONS Connect [ta] OR ONS News [ta] OR Oncogene Res [ta] OR Oncogene [ta] OR Oncol Nurs Forum [ta] OR Oncol Rep [ta] OR Oncol Res [ta] OR Oncol Res Treat [ta] OR Oncologist [ta] OR Oncology Huntingt [ta] OR Oncology [ta] OR Oncotarget [ta] OR Onkologie [ta] OR Open Clin Cancer J [ta] OR Oral Oncol [ta] OR Papillomavirus Res [ta] OR Pathol Oncol Res [ta] OR Pediatr Blood Cancer [ta] OR Pediatr Hematol Oncol [ta] OR Pigment Cell Melanoma Res [ta] OR Pract Radiat Oncol [ta] OR Princess Takamatsu Symp [ta] OR Proc Am Assoc Cancer Res [ta] OR Proc Can Cancer Conf [ta] OR Proc Natl Cancer Conf [ta] OR Prog Clin Cancer [ta] OR Prog Exp Tumor Res [ta] OR Prog Tumor Res [ta] OR Prostate Cancer Prostatic Dis [ta] OR Psychooncology [ta] OR Radiat Oncol Investig [ta] OR Radiat Oncol [ta] OR Radiol Oncol [ta] OR Radiother Oncol [ta] OR Recent Results Cancer Res [ta] OR Rep Carcinog Backgr Doc [ta] OR Rev Mex Cir Ginecol Cancer [ta] OR S Afr Cancer Bull [ta] OR Sci Rep Res Inst Tohoku Univ Med [ta] OR Sel Cancer Ther [ta] OR Semin Cancer Biol [ta] OR Semin Oncol Nurs [ta] OR Semin Oncol [ta] OR Semin Radiat Oncol [ta] OR Semin Surg Oncol [ta] OR Semin Urol Oncol [ta] OR Strahlenther Onkol [ta] OR Suppl J Med Oncol Tumor Pharmacother [ta] OR Suppl Tumori [ta] OR Support Cancer Ther [ta] OR Support Care Cancer [ta] OR Surg Oncol Clin N Am [ta] OR Surg Oncol [ta] OR Symp Fundam Cancer Res [ta] OR Target Oncol [ta] OR Technol Cancer Res Treat [ta] OR Thorac Cancer [ta] OR Transl Oncol [ta] OR Tumor Res [ta] OR Tumori [ta] OR Tumour Biol [ta] OR Urol Oncol [ta] OR Vet Comp Oncol [ta] OR Vopr Onkol [ta] OR World J Surg Oncol [ta] OR Z Krebsforsch Klin Onkol Cancer Res Clin Oncol [ta] OR Z Krebsforsch [ta] OR Zhongguo Fei Ai Za Zhi [ta] OR Zhonghua Zhong Liu Za Zhi [ta]		
3	(("Epidemiologic Studies"[mh] OR "epidemiology"[sh] OR "Meta-Analysis"[pt] OR “Case Reports”[pt] OR workmen*[tiab] OR Worker*[tiab] OR "occupational exposure"[mh] OR "Seroepidemiologic Stud*"[tiab] OR "retrospective stud*"[tiab] OR "prospective stud*"[tiab] OR Mortality[tiab] OR "longitudinal"[tiab] OR "follow-up stud*"[tiab] OR "ecological study"[tiab] OR "ecological studies"[tiab] OR "Cross-Sectional"[tiab] OR "Correlation	8382490	RoC Human Epi terms

Set	Search Terms	Retrieval	Concept Group
	stud*"[tiab] OR cohort*[tiab] OR "case-control*"[tiab] OR "cancer registr*"[tiab] OR "case series"[tiab] OR "case referent"[tiab] OR "record link*"[tiab])) OR ((metaanalysis[tiab] OR "case report*"[tiab] OR metaanalyses[tiab] OR "meta-analys*"[tiab] OR "case-crossover"[tiab] OR "case-cross over"[tiab]) NOT medline[sb])		
4	#1 AND #2 AND #3	**8**	Combine Chemical + Cancer + Human Epi

Table A14. PubMed Search Strategy for Animal Cancer Studies

Set	Search Terms	Retrieval	Concept Group
1	"vinyl acetate"[nm] OR "vinyl acetate"[tiab] OR 108-05-4[rn] OR "acetic acid ethenyl ester"[tiab] OR "ethylene acetate"[tiab:~0] OR vinylacetate[tiab]	2495	chemical terms
2	neoplasms OR American Cancer Society OR angiogenesis inducing agents OR antibodies, neoplasm OR antigens, neoplasm OR antineoplastic agents OR antineoplastic protocols OR biomarkers, tumor OR biopsy [mh] OR biopsy [tw] OR bone marrow purging OR bone marrow transplantation OR cancer care facilities OR cancer vaccines OR carcinogenicity tests OR carcinogens OR chemoembolization, therapeutic OR clonal evolution [mh] OR clonal evolution [tw] OR colonography, computed tomographic OR colonoscopy OR colposcopy OR combined modality therapy OR cryosurgery OR cytapheresis OR dna, neoplasm OR drug resistance, neoplasm OR drug screening assays, antitumor OR early detection of cancer OR gene expression regulation, neoplastic OR genes, neoplasm OR graft vs tumor effect OR hematopoietic stem cell transplantation OR hematopoietic stem cell mobilization OR immunotherapy, adoptive OR leukostasis OR lymph node excision OR lymphocytes, tumor-infiltrating OR mammography OR mastectomy OR medical oncology OR metastasectomy OR mohs surgery OR myelodysplastic-myeloproliferative diseases OR neoplasm grading OR neoplasm proteins OR neoplasm staging OR neoplasm transplantation OR neoplastic processes OR neoplastic stem cells OR oncogene fusion OR oncogenic viruses OR oncology nursing OR oncology service, hospital OR oncolytic viruses OR papanicolaou test [mh] OR papillomavirus vaccines OR peripheral blood stem cell transplantation OR polyomavirus OR radiotherapy OR radiotherapy planning, computer assisted OR rna, neoplasm OR second-look surgery OR SEER program OR stem cell transplantation [mh:noexp] OR transplantation conditioning OR tumor cells, cultured OR tumor escape OR tumor lysis syndrome OR tumor necrosis factors OR receptors, tumor necrosis factor OR tumor necrosis factor receptor-associated peptides and proteins OR ultrasonography, mammary OR AACR OR AJCC [tw] OR (ASCO NOT fungi) OR IARC OR "National Cancer Institute (U.S.)" [mh] OR UICC OR aCML [tw] OR AGCUS [tw] OR AILD [tw] OR AML [tw] OR ANLL [tw] OR ASCUS [tw] OR ATLL [tw] OR BRCA [tw] OR BRCA1 [tw] OR BRCA2 [tw] OR CIN [tw] OR CLL [tw] OR CMML [tw] OR CMPD [tw] OR ECCL [tw] OR EGIST [tw] OR FMTC [tw] OR GLNH [tw] OR HNPCC [tw] OR HNSCC [tw] OR HPV [tw] OR HSIL [tw] OR ICD O [tw] OR JCML [tw] OR JMML [tw] OR LGLL [tw] OR MGUS [tw] OR MLH1[tw] OR MPD [tw] OR MSH2[tw] OR NSCLC [tw] OR RAEB [tw] OR RCMD [tw] OR SCLC [tw] OR VOD [tw] OR 5q syndrome [tw] OR BCR ABL [tw] OR c erbB 2 [tw] OR c erbB2 [tw] OR carney complex [tw] OR cone biopsy [tw] OR denys drash [tw]	7356145	PubMed Cancer terms

	OR essential thrombocythemia [tw] OR estrogen receptor negative [tw] OR estrogen receptor positive [tw] OR li fraumeni [tw] OR meigs syndrome [tw] OR molar pregnancy [tw] OR mycosis fungoides [tw] OR peutz jeghers [tw] OR sentinel lymph node [tw] OR sezary syndrome [tw] OR struma ovarii [tw] OR sturge weber [tw] OR zollinger ellison [tw] OR (aberrant [tw] AND crypt [tw] AND foci [tw]) OR ((anti-n-methyl-d-aspartate [tw] OR anti-nmda) AND encephalitis [tw]) OR (barrett [tw] AND esophagus [tw]) OR (gestational [tw] AND trophoblastic [tw]) OR (microsatellite [tw] AND instability [tw]) OR (paget [tw] AND (breast [tw] OR nipple [tw])) OR (polycythemia [tw] AND vera [tw]) OR (radiation [tw] AND therapy [tw]) OR (WAGR [tw] AND syndrome [tw]) OR (pap [tw] AND (smear [tw] OR smears [tw])) OR cervical smear [tw] OR cervical smears [tw] OR pap test [tw] OR pap tests [tw] OR (PSA [tw] AND prostate) OR PSA test [tw] OR PSA testing [tw] OR (prostate [tw] AND specific [tw] AND antigen [tw]) OR acanthoma [tw] OR acanthomas [tw] OR acrochordon [tw] OR acrochordons [tw] OR acrospiroma [tw] OR acrospiromas [tw] OR adamantinoma [tw] OR adamantinomas [tw] OR adenoacanthoma [tw] OR adenoacanthomas [tw] OR adenoameloblastoma [tw] OR adenoameloblastomas [tw] OR adenocanthoma [tw] OR adenocanthomas [tw] OR adenocarcinoma [tw] OR adenocarcinomas [tw] OR adenofibroma [tw] OR adenofibromas [tw] OR adenolipoma [tw] OR adenolipomas [tw] OR adenolymphoma [tw] OR adenolymphomas [tw] OR adenoma [tw] OR adenomas [tw] OR adenomatosis [tw] OR adenomatous [tw] OR adenomyoepithelioma [tw] OR adenomyoepitheliomas [tw] OR adenomyoma [tw] OR adenomyomas [tw] OR adenosarcoma [tw] OR adenosarcomas [tw] OR adenosis [tw] OR aesthesioneuroblastoma [tw] OR aesthesioneuroblastomas [tw] OR ameloblastoma [tw] OR ameloblastomas [tw] OR amyloidoses [tw] OR amyloidosis [tw] OR anaplasia [tw] OR androblastoma [tw] OR androblastomas [tw] OR angioblastoma [tw] OR angioblastomas [tw] OR angioendothelioma [tw] OR angioendotheliomas [tw] OR angioendotheliomatosis [tw] OR angiofibroma [tw] OR angiofibromas [tw] OR angiofibrosarcoma [tw] OR angiogenesis factor [tw] OR angiokeratoma [tw] OR angiokeratomas [tw] OR angioleiomyoma [tw] OR angioleiomyomas [tw] OR angiolipoma [tw] OR angiolipomas [tw] OR angioma [tw] OR angiomas [tw] OR angiomatosis [tw] OR angiomyolipoma [tw] OR angiomyolipomas [tw] OR angiomyoma [tw] OR angiomyomas [tw] OR angiomyxoma [tw] OR angiomyxomas [tw] OR angioreticuloma [tw] OR angioreticulomas [tw] OR angiosarcoma [tw] OR angiosarcomas [tw] OR anticancer [tw] OR anticarcinogenesis [tw] OR anticarcinogenic [tw] OR antimutagenesis [tw] OR antineoplastic [tw] OR antioncogene [tw] OR antioncogenes [tw] OR antitumor [tw] OR antitumors [tw] OR antitumour [tw] OR antitumours [tw] OR apudoma [tw] OR apudomas [tw] OR argentaffinoma [tw] OR argentaffinomas [tw] OR arrhenoblastoma [tw] OR arrhenoblastomas [tw] OR astroblastoma [tw] OR astroblastomas [tw] OR astrocytoma [tw] OR astrocytomas [tw] OR astroglioma [tw] OR astrogliomas [tw] OR atypia [tw] OR baltoma [tw] OR basiloma [tw] OR basilomas [tw] OR biochemotherapies [tw] OR biochemotherapy [tw] OR bioradiotherapy [tw] OR Birt-Hogg-Dube [tw] OR blastoma [tw] OR blastomas [tw] OR Buschke-Lowenstein [tw] OR cachexia [tw] OR cancer [tw] OR cancerous [tw] OR cancers [tw] OR carcinogen [tw] OR carcinogenesis [tw] OR carcinogenic [tw] OR carcinogens [tw] OR carcinoid [tw] OR carcinoma [tw] OR carcinomas [tw] OR carcinomatosis [tw] OR carcinosarcoma [tw] OR carcinosarcomas [tw] OR cavernoma [tw] OR cavernomas [tw] OR cementoma [tw] OR cementomas [tw] OR cerbB2 [tw] OR ceruminoma [tw] OR ceruminomas [tw] OR chemodectoma [tw] OR chemodectomas [tw] OR chemoimmunoradiotherapy [tw] OR chemoimmunotherapies [tw] OR chemoimmunotherapy [tw] OR chemoprevention [tw] OR chemoradiation [tw]		

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	polyhistioma [tw] OR polyhistiomas [tw] OR polyp [tw] OR polyposis [tw] OR polyps [tw] OR porocarcinoma [tw] OR porocarcinomas [tw] OR poroma [tw] OR poromas [tw] OR precancer [tw] OR precancerous [tw] OR preleukaemia [tw] OR preleukaemias [tw] OR preleukemia [tw] OR preleukemias [tw] OR premalignant [tw] OR preneoplastic [tw] OR prolactinoma [tw] OR prolactinomas [tw] OR protooncogene [tw] OR protooncogenes [tw] OR pseudotumor [tw] OR pseudotumors [tw] OR radiochemotherapy [tw] OR radioimmunotherapies [tw] OR radioimmunotherapy [tw] OR reninoma [tw] OR reninomas [tw] OR reticuloendothelioma [tw] OR reticuloendotheliomas [tw] OR reticulohistiocytoma [tw] OR reticulohistiocytomas [tw] OR reticulosis [tw] OR retinoblastoma [tw] OR retinoblastomas [tw] OR rhabdomyoma [tw] OR rhabdomyomas [tw] OR rhabdomyosarcoma [tw] OR rhabdomyosarcomas [tw] OR rhabdosarcoma [tw] OR rhabdosarcomas [tw] OR sarcoma [tw] OR sarcomas [tw] OR sarcomatosis [tw] OR schwannoma [tw] OR schwannomas [tw] OR schwannomatosis [tw] OR seminoma [tw] OR seminomas [tw] OR seminomatous [tw] OR somatostatinoma [tw] OR somatostatinomas [tw] OR somatotropinoma [tw] OR somatotropinomas [tw] OR spermatocytoma [tw] OR spiradenoma [tw] OR spiradenomas [tw] OR spongioblastoma [tw] OR spongioblastomas [tw] OR steatocystoma [tw] OR steatocystomas [tw] OR subependymoma [tw] OR subependymomas [tw] OR syringadenoma [tw] OR syringadenomas [tw] OR syringocystadenoma [tw] OR syringocystadenomas [tw] OR syringoma [tw] OR syringomas [tw] OR teratocarcinoma [tw] OR teratocarcinomas [tw] OR teratoma [tw] OR teratomas [tw] OR thecoma [tw] OR thecomas [tw] OR thymolipoma [tw] OR thymolipomas [tw] OR thymoma [tw] OR thymomas [tw] OR trichilemmoma [tw] OR trichilemmomas [tw] OR trichoadenoma [tw] OR trichoblastoma [tw] OR trichoblastomas [tw] OR trichodiscoma [tw] OR trichodiscomas [tw] OR trichoepithelioma [tw] OR trichoepitheliomas [tw] OR trichofolliculoma [tw] OR trichofolliculomas [tw] OR tricholemmoma [tw] OR tricholemmomas [tw] OR tumor [tw] OR tumorgenesis [tw] OR tumorgenic [tw] OR tumorigenesis [tw] OR tumorigenic [tw] OR tumorogenesis [tw] OR tumorogenic [tw] OR tumors [tw] OR tumour [tw] OR tumours [tw] OR vipoma [tw] OR vipomas [tw] OR waldenstrom [tw] OR waldenstroms [tw] OR xanthoastrocytoma [tw] OR xanthoastrocytomas [tw] OR xanthofibroma [tw] OR xanthofibromas [tw] OR xanthogranuloma [tw] OR xanthogranulomas [tw] OR xanthoma [tw] OR xanthomas [tw] OR xanthosarcoma [tw] OR xanthosarcomas [tw] OR Acta Oncol [ta] OR Acta Radiol Oncol Radiat Phys Biol [ta] OR Acta Radiol Oncol [ta] OR Adv Cancer Res [ta] OR Adv Immun Cancer Ther [ta] OR Ai Zheng [ta] OR Am J Cancer [ta] OR Am J Clin Oncol [ta] OR Am Soc Clin Oncol Educ Book [ta] OR Anal Cell Pathol [ta] OR Ann Oncol [ta] OR Ann Surg Oncol [ta] OR Anti cancer Drugs [ta] OR Anticancer Agents Med Chem [ta] OR Anticancer Drug Des [ta] OR Anticancer Res [ta] OR Asia Pac J Clin Oncol [ta] OR BMC Cancer [ta] OR Baillieres Clin Oncol [ta] OR Biochim Biophys Acta [ta] OR Blood Cancer J [ta] OR Br J Cancer Suppl [ta] OR Br J Cancer [ta] OR Brain Tumor Pathol [ta] OR Breast Cancer Res Treat [ta] OR Breast Cancer Res [ta] OR Breast Cancer [ta] OR Breast J [ta] OR Bull Assoc Fr Etud Cancer [ta] OR Bull Cancer Radiother [ta] OR Bull Cancer [ta] OR CA Cancer J Clin [ta] OR Can J Oncol [ta] OR Can Oncol Nurs J [ta] OR Cancer Biochem Biophys [ta] OR Cancer Biol Ther [ta] OR Cancer Biomark [ta] OR Cancer Biother Radiopharm [ta] OR Cancer Biother [ta] OR Cancer Bull [ta] OR Cancer Causes Control [ta] OR Cancer Cell Int [ta] OR Cancer Cell [ta] OR Cancer Cells [ta] OR Cancer Chemother Biol Response Modif [ta] OR Cancer Chemother Pharmacol [ta] OR Cancer Chemother Rep 2 [ta] OR Cancer Chemother Rep 3 [ta] OR Cancer Chemother Rep [ta] OR Cancer Clin Trials [ta] OR Cancer Commun [ta] OR "Cancer Commun (Lond)" [ta] OR Cancer Control [ta] OR Cancer Cytol [ta] OR Cancer		

	Cytopathol [ta] OR Cancer Detect Prev Suppl [ta] OR Cancer Detect Prev [ta] OR Cancer Discov [ta] OR Cancer Drug Deliv [ta] OR Cancer Epidemiol Biomarkers Prev [ta] OR Cancer Epidemiol [ta] OR Cancer Gene Ther [ta] OR Cancer Genet [ta] OR Cancer Genet Cytogenet [ta] OR Cancer Genomics Proteomics [ta] OR Cancer Imaging [ta] OR Cancer Immun [ta] OR Cancer Immunol Immunother [ta] OR Cancer Immunol Res [ta] OR Cancer Inform [ta] OR Cancer Invest [ta] OR Cancer J Sci Am [ta] OR Cancer J [ta] OR Cancer Lett [ta] OR Cancer Med [ta] OR Cancer Metastasis Rev [ta] OR Cancer Microenviron [ta] OR Cancer Nurs [ta] OR Cancer Pract [ta] OR Cancer Prev Control [ta] OR Cancer Prev Res Phila [ta] OR Cancer Radiother [ta] OR Cancer Res Treat [ta] OR Cancer Res [ta] OR Cancer Sci [ta] OR Cancer Surv [ta] OR Cancer Treat Rep [ta] OR Cancer Treat Res [ta] OR Cancer Treat Res Commun [ta] OR Cancer Treat Rev [ta] OR Cancer [ta] OR Carcinogenesis [ta] OR Cell Growth Differ [ta] OR Cell Oncol Dordr [ta] OR Chin Clin Oncol [ta] OR Chin J Cancer [ta] OR Chin J Cancer [ta] OR Clin Breast Cancer [ta] OR Clin Cancer Res [ta] OR Clin Colorectal Cancer [ta] OR Clin Exp Metastasis [ta] OR Clin J Oncol Nurs [ta] OR Clin Lymphoma Myeloma Leuk [ta] OR Clin Lymphoma [ta] OR Clin Oncol R Coll Radiol [ta] OR Clin Oncol [ta] OR Clin Transl Oncol [ta] OR CNS Oncol [ta] OR Contemp Oncol [ta] OR Crit Rev Oncog [ta] OR Crit Rev Oncol Hematol [ta] OR Curr Cancer Drug Targets [ta] OR Curr Oncol Rep [ta] OR Curr Oncol [ta] OR Curr Opin Oncol [ta] OR Curr Probl Cancer [ta] OR Curr Treat Options Oncol [ta] OR Dimens Oncol Nurs [ta] OR Drug Resist Updat [ta] OR Eksp Onkol [ta] OR Endocr Relat Cancer [ta] OR Eur J Cancer B Oral Oncol [ta] OR Eur J Cancer Care Engl [ta] OR Eur J Cancer Clin Oncol [ta] OR Eur J Cancer Prev [ta] OR Eur J Cancer [ta] OR Eur J Gynaecol Oncol [ta] OR Eur J Surg Oncol [ta] OR Front Radiat Ther Oncol [ta] OR Future Oncol [ta] OR Gan No Rinsho [ta] OR Gan To Kagaku Ryoho [ta] OR Gastric Cancer [ta] OR Gastrointest Cancer Res [ta] OR Genes Chromosomes Cancer [ta] OR Gulf J Oncolog [ta] OR Gynecol Oncol [ta] OR Head Neck Oncol [ta] OR Hematol Oncol Clin North Am [ta] OR Hematol Oncol Stem Cell Ther [ta] OR Hematol Oncol [ta] OR Hered Cancer Clin Pract [ta] OR Horm Cancer [ta] OR IARC Monogr Eval Carcinog Risk Chem Hum Suppl [ta] OR IARC Monogr Eval Carcinog Risk Chem Hum [ta] OR IARC Monogr Eval Carcinog Risk Chem Man [ta] OR IARC Monogr Eval Carcinog Risks Hum Suppl [ta] OR IARC Monogr Eval Carcinog Risks Hum [ta] OR IARC Sci Publ [ta] OR Important Adv Oncol [ta] OR Indian J Cancer [ta] OR Infect Agent Cancer [ta] OR Innov Oncol Nurs [ta] OR Int Adv Surg Oncol [ta] OR Int J Biol Markers [ta] OR Int J Cancer Suppl [ta] OR Int J Cancer [ta] OR Int J Clin Oncol [ta] OR Int J Gastrointest Cancer [ta] OR Int J Gynecol Cancer [ta] OR Int J Hyperthermia [ta] OR Int J Oncol [ta] OR Int J Radiat Oncol Biol Phys [ta] OR Int J Surg Oncol [ta] OR Integr Cancer Ther [ta] OR Invasion Metastasis [ta] OR Invest New Drugs [ta] OR J Adolesc Young Adult Oncol [ta] OR J Assoc Pediatr Oncol Nurses [ta] OR J Cancer Educ [ta] OR J Cancer Epidemiol Prev [ta] OR J Cancer Res Clin Oncol [ta] OR J Cancer Res [ta] OR J Cancer Surviv [ta] OR J Chemother [ta] OR J Clin Oncol [ta] OR J Community Support Oncol [ta] OR J Dermatol Surg Oncol [ta] OR J Egypt Natl Canc Inst [ta] OR J Environ Pathol Toxicol Oncol [ta] OR J Exp Clin Cancer Res [ta] OR J Exp Ther Oncol [ta] OR J Geriatr Oncol [ta] OR J Gynecol Oncol [ta] OR J Hematol Oncol [ta] OR J Immunother Emphasis Tumor Immunol [ta] OR J Immunother [ta] OR J Mammary Gland Biol Neoplasia [ta] OR J Med Imaging Radiat Oncol [ta] OR J Natl Cancer Inst Monogr [ta] OR J Natl Cancer Inst [ta] OR J Natl Compr Canc Netw [ta] OR J Neurooncol [ta] OR J Oncol Manag [ta] OR J Oncol Pract [ta] OR J Oncol [ta] OR J Pediatr Hematol Oncol [ta] OR J Pediatr Oncol Nurs [ta] OR J Soc Integr Oncol [ta] OR J Support Oncol [ta] OR J Surg Oncol Suppl [ta] OR J		

	Surg Oncol [ta] OR J Thorac Oncol [ta] OR Jaarb Kankeronderz Kankerbestrijd Ned [ta] OR JAMA Oncol [ta] OR JCO Clin Cancer Inform [ta] OR Jpn J Cancer Res [ta] OR Jpn J Clin Oncol [ta] OR Klin Onkol [ta] OR Lancet Oncol [ta] OR Leuk Lymphoma [ta] OR Leuk Res [ta] OR Leukemia [ta] OR Lung Cancer [ta] OR Lutte Cancer [ta] OR Magy Onkol [ta] OR Med Oncol Tumor Pharmacother [ta] OR Med Oncol [ta] OR Med Pediatr Oncol Suppl [ta] OR Med Pediatr Oncol [ta] OR Melanoma Res [ta] OR Mol Cancer Res [ta] OR Mol Cancer Ther [ta] OR Mol Cancer [ta] OR Mol Oncol [ta] OR Monogr Neoplast Dis Var Sites [ta] OR NCI Monogr [ta] OR Nat Rev Cancer [ta] OR Nat Rev Clin Oncol [ta] OR Natl Cancer Inst Monogr [ta] OR Natl Cancer Inst Res Rep [ta] OR Neoplasia [ta] OR Neoplasma [ta] OR Neuro oncol [ta] OR Nippon Gan Chiryo Gakkai Shi [ta] OR Noshuyo Byori [ta] OR Nutr Cancer [ta] OR ONS Connect [ta] OR ONS News [ta] OR Oncogene Res [ta] OR Oncogene [ta] OR Oncol Nurs Forum [ta] OR Oncol Rep [ta] OR Oncol Res [ta] OR Oncol Res Treat [ta] OR Oncologist [ta] OR Oncology Huntingt [ta] OR Oncology [ta] OR Oncotarget [ta] OR Onkologie [ta] OR Open Clin Cancer J [ta] OR Oral Oncol [ta] OR Papillomavirus Res [ta] OR Pathol Oncol Res [ta] OR Pediatr Blood Cancer [ta] OR Pediatr Hematol Oncol [ta] OR Pigment Cell Melanoma Res [ta] OR Pract Radiat Oncol [ta] OR Princess Takamatsu Symp [ta] OR Proc Am Assoc Cancer Res [ta] OR Proc Can Cancer Conf [ta] OR Proc Natl Cancer Conf [ta] OR Prog Clin Cancer [ta] OR Prog Exp Tumor Res [ta] OR Prog Tumor Res [ta] OR Prostate Cancer Prostatic Dis [ta] OR Psychooncology [ta] OR Radiat Oncol Investig [ta] OR Radiat Oncol [ta] OR Radiol Oncol [ta] OR Radiother Oncol [ta] OR Recent Results Cancer Res [ta] OR Rep Carcinog Backgr Doc [ta] OR Rev Mex Cir Ginecol Cancer [ta] OR S Afr Cancer Bull [ta] OR Sci Rep Res Inst Tohoku Univ Med [ta] OR Sel Cancer Ther [ta] OR Semin Cancer Biol [ta] OR Semin Oncol Nurs [ta] OR Semin Oncol [ta] OR Semin Radiat Oncol [ta] OR Semin Surg Oncol [ta] OR Semin Urol Oncol [ta] OR Strahlenther Onkol [ta] OR Suppl J Med Oncol Tumor Pharmacother [ta] OR Suppl Tumori [ta] OR Support Cancer Ther [ta] OR Support Care Cancer [ta] OR Surg Oncol Clin N Am [ta] OR Surg Oncol [ta] OR Symp Fundam Cancer Res [ta] OR Target Oncol [ta] OR Technol Cancer Res Treat [ta] OR Thorac Cancer [ta] OR Transl Oncol [ta] OR Tumor Res [ta] OR Tumori [ta] OR Tumour Biol [ta] OR Urol Oncol [ta] OR Vet Comp Oncol [ta] OR Vopr Onkol [ta] OR World J Surg Oncol [ta] OR Z Krebsforsch Klin Onkol Cancer Res Clin Oncol [ta] OR Z Krebsforsch [ta] OR Zhongguo Fei Ai Za Zhi [ta] OR Zhonghua Zhong Liu Za Zhi [ta]		
3	("Animals, Genetically Modified"[mh] OR "Animals, Inbred Strains"[mh] OR "Chimera"[mh] OR "Animals, Laboratory"[mh] OR "models, animal"[mh] OR animals[mh:noexp] OR "animal experimentation"[mh] OR "murinae"[mh]) OR ("animal stud*"[tiab] OR "animal model*"[tiab] OR ape[tiab] OR apes[tiab] OR balb[tiab] OR bonobo*[tiab] OR bovine[tiab] OR C57[tiab] OR C57bl[tiab] OR callithrix[tiab] OR canis[tiab] OR capra[tiab] OR capuchin*[tiab] OR cattle[tiab] OR cavia[tiab] OR chicken[tiab] OR chickens[tiab] OR chimpanzee*[tiab] OR chinchilla*[tiab] OR cow[tiab] OR cows[tiab] OR cricetinae[tiab] OR "danio rerio"[tiab] OR equus[tiab] OR felis[tiab] OR ferret[tiab] OR ferrets[tiab] OR fish[tiab] OR "flying fox"[tiab] OR "Fruit bat"[tiab] OR gibbon*[tiab] OR goat[tiab] OR goats[tiab] OR guppy[tiab] OR horse[tiab] OR horses[tiab] OR "in vivo"[tiab] OR jird[tiab] OR jirds[tiab] OR leontopithecus[tiab] OR "long-evans"[tiab] OR macaque*[tiab] OR marmoset*[tiab] OR medaka[tiab] OR merione[tiab] OR meriones[tiab] OR muridae[tiab] OR murinae[tiab] OR "Mustela putorius"[tiab] OR nomascus[tiab] OR "non human primate*"[tiab] OR "offspring"[tiab] OR orangutan*[tiab] OR "pan paniscus"[tiab] OR "pan troglodytes"[tiab] OR	8180043	RoC Experimental Animals Terms

	pig[tiab] OR piglet*[tiab] OR pigs[tiab] OR polecat*[tiab] OR quail[tiab] OR "rainbow trout"[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodentia[tiab] OR rodents[tiab] OR saguinus[tiab] OR sheep[tiab] OR sheeps[tiab] OR siamang*[tiab] OR "Sprague-Dawley"[tiab] OR swine[tiab] OR swines[tiab] OR symphalangus[tiab] OR tamarin*[tiab] OR vervet*[tiab] OR wistar[tiab] OR "wood mouse"[tiab] OR zebrafish[tiab]) OR ((boar[tiab] OR boars[tiab] OR cat[tiab] OR cats[tiab] OR dog[tiab] OR dogs[tiab] OR gerbil*[tiab] OR "guinea pig*"[tiab] OR hamster[tiab] OR hamsters[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR "pongo pygmaeus"[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR sow[tiab] OR sows[tiab]) NOT medline[sb]) OR ("invertebrate*"[tiab] OR "c elegans"[tiab] OR "Caenorhabditis elegans"[tiab] OR "Caenorhabditis elegans"[mh] OR "d melanogaster"[tiab] OR "Drosophila"[tiab] OR "Drosophila"[mh] OR "g mellonella"[tiab] OR "galleria mellonella"[tiab] OR "artemia salina"[tiab] OR "bombyx"[tiab] OR "bombyx"[mh] OR "silkworm*"[tiab] OR "planarian*"[tiab] OR "dugesia japonica"[tiab]) OR (("in vitro"[tiab] OR "in vitro techniques"[mh] OR "cell line*"[tiab]) AND "animals"[mh:noexp])		
4	#1 AND #2 AND #3	134	Combine Chemical + Cancer terms + Animals terms
5	#4 NOT (drug[tiab] OR drugs[tiab] OR therapy[ti] OR drug therapy[mh] OR acetylation[tiab] OR "ethylene vinyl acetate"[tiab] OR "polyethylene vinyl acetate"[tiab] OR "poly ethylene vinyl acetate"[tiab] OR "co vinyl acetate"[tiab] OR "drug implants"[mh] OR "administration and dosage"[sh] OR delivery[ti])	**50**	remove drug delivery & copolymers

Table A15. PubMed Search Strategy for Pharmacokinetics and Metabolism (ADME) Studies

Set	Search Terms	Retrieval	Concept Group
1	"vinyl acetate"[nm] OR "vinyl acetate"[tiab] OR 108-05-4[rn] OR "acetic acid ethenyl ester"[tiab] OR "ethylene acetate"[tiab:~0] OR vinylacetate[tiab]	2495	chemical terms
2	(("Volume of Distribution"[tiab] OR "Toxicokinetics"[mh] OR "tissue distribut*"[tiab] OR "Renal Elimination"[mh] OR "protein bound"[tiab] OR "protein bind*"[tiab] OR "plasma protein"[tiab] OR "Pharmacokinetics"[mh] OR "Metabolism"[mh] OR "kinetic"[tiab] OR "Intestinal Elimination"[mh] OR "Hepatobiliary Elimination"[mh] OR "Hepatobiliary"[tiab] OR "enterohepatic"[tiab] OR "entero-hepatic"[tiab] OR "Distribution volume"[tiab] OR "cellular clearance"[tiab] OR "cell clearance"[tiab] OR "Biotransformation"[tiab] OR "ADME"[tiab] OR "absorptive"[tiab] OR "PBPK"[tiab] OR "toxicodynamic*"[tiab] OR ("Skin"[tiab] AND "absorption"[tiab]) OR ("Oral"[tiab] AND "absorption"[tiab]) OR	3095502	RoC ADME

	("Injection"[tiab] AND "absorption"[tiab]) OR ("Gavage"[tiab] AND "absorption"[tiab]) OR ("Dietary"[tiab] AND "absorption"[tiab]) OR ("Dermal"[tiab] AND "absorption"[tiab])) OR (("urine"[tiab] OR "Urination"[tiab] OR "toxicokinetic*"[tiab] OR "Pharmacokinetic*"[tiab] OR "Metabolite*"[tiab] OR "metabolism"[tiab] OR "Metabolic* "[tiab] OR "feces"[tiab] OR "fecal"[tiab] OR "excretion"[tiab] OR "defecation"[tiab] OR "biliary"[tiab] OR "Bile"[tiab]) NOT Medline[sb]))		
3	#1 AND #2	462	combine chemical with ADME
4	(drug[tiab] OR drugs[tiab] OR therap*[tiab] OR drug therapy[mh] OR acetylation[tiab] OR "ethylene vinyl acetate"[tiab] OR "polyethylene vinyl acetate"[tiab] OR "poly ethylene vinyl acetate"[tiab] OR "co vinyl acetate"[tiab] OR "poly vinyl acetate"[tw] OR "poly vinylacetate"[tw] OR "drug implants"[mh] OR "administration and dosage"[sh] OR delivery[ti] OR synthesis[tiab] OR chemistry[sh] OR "copolymer*"[ti] OR "polymer*"[ti] OR cataly*[ti])	9865048	unwanted concepts: drug delivery, copolymers, chemical synthesis
5	#3 NOT #4	**34**	remove unwanted terms

Table A16. PubMed Search Strategy for Key Characteristics of Carcinogens and Mechanistic Concepts

Set	Search Terms	Retrieval	Concept Group
1	"vinyl acetate"[nm] OR "vinyl acetate"[tiab] OR 108-05-4[rn] OR "acetic acid ethenyl ester"[tiab] OR "ethylene acetate"[tiab:~0] OR vinylacetate[tiab]	2495	chemical terms

Set	Search Terms	Retrieval	Concept Group
2	adduct-formation[tiab] OR "DNA Adducts"[mh] OR DNA-Adduct*[tiab] OR electrophile[tiab] OR electrophilic[tiab] OR dna-alkylating-agent*[tiab] OR "Comet Assay"[mh] OR “germ-line mutation”[MeSH] OR "Mutagenesis"[mh] OR "Mutagenicity tests"[mh] OR "Sister-chromatid exchange"[mh] OR "Mutation"[mh] OR Ames-Assay[tiab] OR Ames-test[tiab] OR Bacterial-Reverse-Mutation-Assay[tiab] OR Clastogen*[tiab] OR DNA-Repair*[tiab] OR Genetic-toxicology[tiab] OR hyperploid[tiab] OR micronucleus-test[tiab] OR tetraploid[tiab] OR Chromosome-aberrations[tiab] OR DNA damage[tiab] OR Mutation[tiab] OR chromosome-translocations[tiab] OR DNA protein crosslinks[tiab] OR DNA-damag*[tiab] OR DNA-inhibit*[tiab] OR Micronuclei[tiab] OR Micronucleus[tiab] OR Mutagens[tiab] OR Strand-break*[tiab] OR Unscheduled-DNA-synthes*[tiab] OR chromosomal-aberration[tiab] OR chromosome-aberration[tiab] OR chromosomal-aberrations[tiab] OR chromosomal-abnormalit*[tiab] OR chromosome-abnormalit*[tiab] OR genotoxic[tiab] OR “sos response, genetics”[MeSH] OR "Polyploidy"[mh] OR "Genomic Instability"[mh] OR "DNA Repair"[mh] OR "Aneuploidy"[mh] OR (DNA[tiab] AND Crosslink[tiab]) OR microsatellite-instability[tiab] OR chromosomal-instability[tiab] OR binucleation[tiab] OR binucleated[tiab] OR "histone deacetylases"[mh] OR "RNA, Small Interfering"[mh] OR epigenotype[tiab] OR proteasome[tiab] OR "Free Radicals"[mh] OR "Reactive Oxygen Species"[mh] OR "Oxidative stress"[mh] OR "Electron Transport"[mh] OR Oxidative-damage*[tiab] OR reactive-nitrogen-species[tiab] OR superoxide-radical*[tiab] OR hydroxyl-radical[tiab] OR glutathione-deplet*[tiab] OR "C-reactive protein"[mh] OR "eosinophils"[mh] OR (fibrinogen[tiab] AND Inflammation[tiab]) OR chronic-inflammation[tiab] OR chronically-inflamed[tiab] OR infiltrating-leukocyt*[tiab] OR inflammatory-leukocyte[tiab] OR inflammatory-leukocytes[tiab] OR leukocyte-infiltrat*[tiab] OR pro-inflammatory[tiab] OR proinflammatory[tiab] OR macrophage-recruitment[tiab] OR "Cytotoxicity, Immunologic"[mh] OR "Immunologic Factors"[mh] OR "Immunomodulation"[mh] OR "B-Cell Activation Factor Receptor"[mh] OR Antigenic Modulation[mh] OR "B-Cell Activating Factor"[mh] OR Immunologic Factors[pa] OR b-cell-activation[tiab] OR immune surveillance[tiab] OR immune-suppress*[tiab] OR immunostimulant[tiab] OR immune-activation[tiab] OR immunodeficien*[tiab] OR somatic-hypermutation[tiab] OR immune-activation[tiab] OR immune-system-activation[tiab] OR Chronic-antigenic-stimulation[tiab] OR immunosuppress*[tiab] OR "Receptors, Aryl Hydrocarbon"[mh] OR "Transcriptional Activation"[mh] OR Aryl-hydrocarbon-receptor*[tiab] OR receptor-mediat*[tiab] OR transcription-factor*[tiab] OR transcriptional-activat*[tiab] OR Xenobiotic-sensor*[tiab] OR xenosensor*[tiab] OR Ah-receptor*[tiab] OR alternative-lengthening-of-telomere*[tiab] OR cellular-Immortalization[tiab] OR p53-inactivat*[tiab] OR p53-inhibit*[tiab] OR p53-delet*[tiab] OR pRb-inactivat*[tiab] OR pRb-inhibit*[tiab] OR pRb-delet*[tiab] OR Rb/p16INK4a inactiv*[tiab] OR retinoblastoma-protein[tiab] OR senescent[tiab] OR senescence[tiab] OR "Angiogenesis Modulating Agents"[mh] OR "Angiogenesis Inducing Agents"[pa] OR "Angiogenesis Inducing Agents"[mh] OR "Neovascularization, Pathologic"[mh] OR "Cell Hypoxia"[mh] OR angiogenic[tiab] OR cellular-energetics[tiab] OR hypoxic-cell*[tiab] OR cell-hypoxia[tiab] OR cellular-hypoxia[tiab] OR "Apoptosis"[mh] OR "Cytotoxicity, Immunologic"[mh] OR "Caspases"[mh] OR "autophagy"[mh] OR "necrosis" [mh] OR "Autolysis"[mh] OR survivin[tiab] OR Cytotoxin[tiab] OR Caspases[tiab] OR "Cell	6721106	RoC Cancer KC

Set	Search Terms	Retrieval	Concept Group
	Proliferation"[mh] OR "homeostasis"[mh] OR "Cyclin-Dependent Kinases"[mh] OR "Cyclin-Dependent Kinase Inhibitor Proteins"[mh] OR "mitogens"[mh] OR "Mitogens"[pa] OR cell-cycle-control*[tiab] OR mitotic-checkpoint*[tiab] OR hepatocellular-proliferation[tiab] OR Cytogenesis[tiab] OR Cytogenic[tiab] OR cellular-replication*[tiab] OR hyperplasia[tiab] OR Neoplasia[tiab] OR mitogenesis[tiab] OR Comet-assay[tiab] OR Mutagenic[tiab] OR Mutagenicity[tiab] OR mutations[tiab] OR chromosomal-aberration-test[tiab] OR Sister-chromatid-exchange[tiab] OR SOS-response[tiab] OR Polyploid*[tiab] OR Genomic-Instability[tiab] OR DNA-Repair*[tiab] OR Aneuploid*[tiab] OR deacetylation[tiab] OR histone-deacetylase*[tiab] OR gene-expression[tiab] OR electron-transport-chain*[tiab] OR reactive-oxygen-species[tiab] OR Oxidative-stress*[tiab] OR free-radical*[tiab] OR C-reactive-protein*[tiab] OR eosinophil*[tiab] OR autoimmunity[tiab] OR Immunomodulation[tiab] OR Immune-modulation[tiab] OR cellular-homeostasis[tiab] OR Cell-Proliferat*[tiab] OR Cellular-Proliferat*[tiab] OR cyclin-dependent-kinase*[tiab] OR cyclin-dependent-kinase-inhibit*[tiab] OR mitogens[tiab] OR mitogen[tiab] OR Apoptosis[tiab] OR autophagy[tiab] OR necrosis [tiab] OR autolysis[tiab] OR angiogenesis[tiab] OR (“Epigenesis, genetic”[mh] OR “Epigenomics”[mh] OR epigen*[tiab] OR epitranscriptome [tiab] OR epiallel*[tiab] OR epimutat*[tiab] OR “epigenetic mark*”[tiab] OR Genomic imprinting[mh] OR (imprint*[tiab] AND (gene[tiab] OR genes[tiab] OR genetic[tiab] OR genomic[tiab] OR loci[tiab])) OR dna-modification[tiab] OR Gene silencing[mh] OR "gene silencing"[tiab] OR “gene silencer”[tiab] OR "gene activation"[tiab] OR "gene inactivation"[tiab] OR “Polycomb group proteins”[tiab] OR “PcG silencing”) OR (“DNA Methylation”[mh] OR “DNA Methylation”[tiab] OR “Promoter methylation”[tiab] OR ((DNA[mh] OR DNA[tiab]) AND (genome, human[mh] OR "genome wide association study"[mh] OR epigenesis, genetic[mh] OR epigenomics[mh] OR genome-wide*[tiab] OR GWAS[tiab] OR genome-scale[tiab] OR Genome[tiab] OR "epigenome-wide"[tiab] OR EWAS[tiab] OR "whole genome"[tiab] OR Methylation-profil*[tiab] OR methylation-pattern*[tiab] OR Methylom*[tiab] OR (("CpG islands"[mh] OR CpG[tiab] OR CpGs[tiab] OR CPG's[tiab] OR non-CG[tiab] OR non-CPG[tiab]) AND (methylat*[tiab])) OR methylat*[tiab] OR hemimethylat*[tiab] OR hypermethylat*[tiab] OR hypomethylat*[tiab] OR demethylat*[tiab] OR nonmethylat*[tiab] OR remethylat*[tiab] OR unmethylat*[tiab] OR Methyltransferases[mh] OR “DNA modification methylases”[mh] OR methylas*[tiab] OR demethylas*[tiab] OR methyltransferase*[tiab] OR methyl-transferase*[tiab] OR 5-methylcytosine[mh] OR "5-methylcytosine"[tiab] OR 5-methyl-cytosine[tiab] OR 5mc[tiab] OR 5meC[tiab] OR "5 hydroxymethylcytosine"[tiab] OR 5hmc[tiab] OR Hydroxymethylat*[tiab] OR 5-hydroxymethylcytosine[tiab] OR 5-hydroxy-methylcytosine[tiab] OR 5-hydroxymethyl-cytosine[tiab] OR 5hmC[tiab] OR “5-Formylcytosine”[tiab] OR “5-Carboxylcytosine”[tiab] OR Methyladenine [tiab] OR Methylcytosine [tiab] OR Hydroxymethylcytosine [tiab] OR Formylcytosine [tiab] OR Carboxylcytosine [tiab] OR methyladenosine OR methylcytosine OR methylguanosine OR ((nucleotide*[tiab] OR cytosine[mh] OR cytosine*[tiab] OR Alu[tiab] OR genes[tiab] OR genom*[tiab]) AND (methylat*[tiab])))) OR ((RNA[mh] OR RNA[tiab]) AND (Queuosine OR Pseudouridine OR Methyladenosine OR Methylcytidine OR Methylguanosine OR Methylinosine OR Methyluridine OR Ribosyladenosine OR Ribosylguanosine OR Formyladenosine OR Formylcytidine OR methylcytosine OR cap methylation OR uridylation OR inosine editing)) OR (histone marks OR histone markers OR histone-tail-		

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	modification [tiab] OR histone-tail-modifications [tiab] OR methylation-associated-silencing [tiab] OR "histone modification"[tiab] OR ((Histones[mh] OR Histone code[mh] OR histone* [tiab]) AND (methylat*[tiab] OR methylase*[tiab] OR hypermethyl*[tiab] OR hypomethyl*[tiab] OR acetylation[mh] OR acetylase*[tiab] OR acetylat*[tiab] OR acetyltransferases[mh] OR acetyltransferase*[tiab] OR acetyl-transferase*[tiab] OR deacetyla*[tiab] OR de-acetylat*[tiab] OR HDAC[tiab] OR ubiquitination[tiab] OR ubiquitination[mh] OR proteasome OR ubiquitins[mh] OR “phosphorylation”[tiab] OR phosphorylation [MeSH] OR "lysine crotonylation”[tiab] OR lysine [MeSH] OR butyrylation OR butylation OR propionylation OR (("tyrosine hydroxylation”[tiab] OR Tyrosine [mesh]) AND (Hydroxylation [mesh])) OR "biotinylation”[tiab] OR Biotin [mesh] OR Biotinylation [mesh] OR "neddylation”[tiab] OR NEDD8 Protein [mesh] OR Sumoylation [mesh] OR SUMO-1 Protein [Mesh] OR " O-Linked N-acetylglucosamine”[tiab] OR “O-GlcNAc”[tiab] OR Acetylglucosamine [mesh] OR N-Acetylglucosaminyltransferases [mesh] OR ((ADP-Ribosylation [mesh] OR “Adenosine Diphosphate” [mesh]) AND Ribose [mesh]) OR (("proline isomerization”[tiab] OR Proline [mesh]) AND Isomerism [mesh]) OR "citrullination”[tiab] OR “imination”[tiab] OR Citrulline [mesh] OR Protein-Arginine Deiminases [mesh] OR Citrullination [mesh] OR "N-formylation"))) OR (((Chromatin[mh] OR chromatin[tiab] OR nucleosom*[tiab]) AND (remodel*[tiab])) OR “chromatin-organization” [tiab] OR “Chromatin modification”[tiab] OR “open chromatin”) OR (("Euchromatin"[MeSH Terms] OR "Euchromatin") OR (open AND ("Chromatin"[MeSH Terms] OR "Chromatin")) OR (("Chromatin"[MeSH Terms] OR "Chromatin") AND relax*) OR ("Heterochromatin"[MeSH Terms] OR "Heterochromatin") OR (("Chromatin"[MeSH Terms] OR "Chromatin") AND compact*) OR (("Chromatin"[MeSH Terms] OR "Chromatin") AND condens*) OR (("Heterochromatin"[MeSH Terms] OR "Heterochromatin") AND constitutive) OR (("Heterochromatin"[MeSH Terms] OR "Heterochromatin") AND facultative) OR (pericentromer* AND DNA) OR (satellite AND DNA) OR (DNA and "transposable elements") OR (tandem AND repeats) OR (interspersed AND repeats)) OR ("Non-coding RNA"[tiab] OR ncRNA*[tiab] OR “RNA Interference” [mh] OR “Guide RNA”[tiab] OR “gRNA”[tiab] OR “Ribonuclease P”[tiab] OR “Rnase P”[tiab] OR “Y RNA”[tiab] OR “Telomerase RNA Component”[tiab] OR “TERC”[tiab] OR “Spliced Leader RNA”[tiab] OR “SL RNA”[tiab] OR lncRNA*[tiab] OR “lncRNA”[tiab] OR “RNA, long noncoding” [MeSH] OR "short interfering RNA"[tiab] OR siRNA*[tiab] OR "small interfering RNA"[tiab] OR “RNA, Small Interfering” [mh] OR “RNA interference”[mh] OR "small silencing RNA"[tiab] OR “small inhibitory"[tiab] OR “small interfering”[tiab] OR “small RNA”[tiab] OR “smallRNA”[tiab] OR “small inhibitory RNA*”[tiab] OR microRNAs[mh] OR miRNA*[tiab] OR microRNA*[tiab] OR "micro RNA"[tiab] OR "micro RNAs"[tiab] OR piRNA*[tiab] OR PiwiRNA*[tiab] OR "piwi-interacting RNA"[tiab] OR “snRNA”[tiab] OR “small nuclear RNA”[tiab] OR “spliceosomal RNA”[tiab] OR “snoRNA”[tiab] OR “small nucleolar RNA”[tiab] OR “SmY RNA”[tiab] OR “Small-Cajal-body-specific RNA”[tiab] OR “scaRNA”[tiab] OR “RNA editing”[tiab] OR “RNA splicing”[tiab] OR “intron retention”[tiab]))		

Set	Search Terms	Retrieval	Concept Group
3	(“Mutation”[Mesh] OR “Cytogenetic Analysis”[Mesh] OR “Mutagens”[Mesh] OR “Oncogenes”[Mesh] OR “Genetic Processes”[All Fields] OR “genomic instability”[MesH] OR chromosom*[All Fields] OR clastogen*[All Fields] OR “genetic toxicology”[All Fields] OR “strand break”[All Fields] OR “unscheduled DNA synthesis”[All Fields] OR “DNA damage”[All Fields] OR “DNA adducts”[All Fields] OR “chromatid”[All Fields] OR micronucle*[All Fields] OR mutagen*[All Fields] OR “DNA repair”[All Fields] OR “DNA fragmentation”[All Fields] OR “DNA cleavage”[All Fields]) OR (“rna”[MeSH] OR “epigenesis, genetic”[MesH] OR rna OR “rna, messenger”[MeSH] OR “rna”[All Fields] OR “messenger rna”[All Fields] OR mrna[All Fields] OR “histones”[MeSH] OR histones[All Fields] OR epigenetic[All Fields] OR miRNA[All Fields] OR methylation [All Fields]) OR (“reactive oxygen species”[MeSH Terms] OR “reactive oxygen species”[All Fields] OR “oxygen radicals”[All Fields] OR “oxidative stress”[MeSH Terms] OR “oxidative”[All Fields] OR “oxidative stress”[All Fields] OR “free radicals”[All Fields]) OR ((chronic[All Fields] AND “inflammation”[MeSH Terms]) OR (chronic inflamm*[All Fields])) OR (Immunosuppression[MH] OR “Killer Cells, Natural”[MH] OR “CD4-Positive TLymphocytes”[MH] OR immunosuppress*[tw] OR immune response*[tw] OR immune function*[tw] OR “immune status”[tw] OR “immune state*”[tw] OR “immune competence”[tw] OR “immune impairment”[tw] OR “immune dysregulation”[tw] OR “humoral immunity”[tw] OR “cell-mediated immunity”[tw] OR NK[tw] OR “Natural Killer”[tw] OR CD4[tw] OR “T4 Cell*”[tw] OR T4 Lymphocyte[tw]) OR (“Mutation”[Mesh] OR “Cytogenetic Analysis”[Mesh] OR “Mutagens”[Mesh] OR “Oncogenes”[Mesh] OR “Genetic Processes”[All Fields] OR “genomic instability”[MesH] OR chromosom*[All Fields] OR clastogen*[All Fields] OR “genetic toxicology”[All Fields] OR “strand break”[All Fields] OR “unscheduled DNA synthesis”[All Fields] OR “DNA damage”[All Fields] OR “DNA adducts”[All Fields] OR “chromatid”[All Fields] OR micronucle*[All Fields] OR mutagen*[All Fields] OR “DNA repair”[All Fields] OR “DNA fragmentation”[All Fields] OR “DNA cleavage”[All Fields]) OR (“rna”[MeSH] OR “epigenesis, genetic”[MesH] OR rna OR “rna, messenger”[MeSH] OR “rna”[All Fields] OR “messenger rna”[All Fields] OR mrna[All Fields] OR “histones”[MeSH] OR histones[All Fields] OR epigenetic[All Fields] OR miRNA[All Fields] OR methylation [All Fields]) OR (“reactive oxygen species”[MeSH Terms] OR “reactive oxygen species”[All Fields] OR “oxygen radicals”[All Fields] OR “oxidative stress”[MeSH Terms] OR “oxidative”[All Fields] OR “oxidative stress”[All Fields] OR “free radicals”[All Fields]) OR ((chronic[All Fields] AND “inflammation”[MeSH Terms]) OR (chronic inflamm*[All Fields])) OR (Immunosuppression[MH] OR “Killer Cells, Natural”[MH] OR “CD4-Positive T Lymphocytes”[MH] OR immunosuppress*[tw] OR immune response*[tw]	6235368	IARC Cancer KC

Set	Search Terms	Retrieval	Concept Group
	OR immune function*[tw] OR “immune status”[tw] OR “immune state*”[tw] OR “immune competence”[tw] OR “immune impairment”[tw] OR “immune dysregulation”[tw] OR “humoral immunity”[tw] OR “cell-mediated immunity”[tw] OR NK[tw] OR “Natural Killer”[tw] OR CD4[tw] OR “T4 Cell*”[tw] OR T4 Lymphocyte[tw]) OR (“Androgen Antagonists”[Mesh:NoExp] OR “Androgen Receptor Antagonists”[Mesh:NoExp] OR “Estrogen Antagonists”[MH] OR “Estrogen Receptor Modulators”[MH:NoExp] OR “Gonadal Hormones”[MH] OR “Thyroid Hormones”[MH] OR “Endocrine Disruptors”[MH] OR “Receptors, Steroid”[MH] OR “Receptors, Cytoplasmic and Nuclear”[MH] OR “Receptors, Aryl Hydrocarbon”[MH] OR Androgen* [tw] OR Estradiol[tw] OR Estrogen* [tw] OR Progesterone[tw] OR Testosterone[tw] OR thyroid[tw] OR “Endocrine disrupt*”[tw] OR “Peroxisome Proliferator-Activated Receptor”[tw] OR PPAR[tw] OR “constitutive androstane receptor”[tw] OR “farnesoid X activated receptor”[tw] OR “liver X receptor”[tw] OR “Retinoid X receptor”[tw] OR “Aryl hydrocarbon receptor”[tw] OR “Ah receptor”[tw]) OR (“Cell Transformation, Neoplastic”[MH:NoExp] OR “Cell Transformation, Viral”[MH] OR Telomere[MH] OR “Telomere Shortening”[MH] OR “Telomere Homeostasis”[MH] OR “cell transformation”[tw] OR “tumorigen transformation”[tw] “tumorigenic transformation”[tw] OR “neoplastic transformation”[tw] OR “carcinogen transformation”[tw] OR “carcinogenic transformation”[tw] OR “viral transformation”[tw] OR immortalization[tw] OR Telomer* [tw]) OR (“Cell Proliferation”[MH] OR “DNA Replication”[MH] OR “Cell Cycle”[MH] OR Hyperplasia[MH] OR Metaplasia[MH:NoExp] OR “Neovascularization, Pathologic”[MH:NoExp] OR Apoptosis[MH] OR “Angiogenesis Modulating Agents”[MH:NoExp] OR “Angiogenesis Inducing Agents”[MH] OR “Heat-Shock Proteins”[MH] OR “Extracellular Matrix”[MH:NoExp] OR “Cell proliferation”[tw] OR “Cellular proliferation”[tw] OR “Cell multiplication”[tw] OR “Cell division”[tw] OR “Proliferative activity”[tw] OR “Sustained proliferation”[tw] OR “DNA replication”[tw] OR “DNA synthesis”[tw] OR “tumor growth”[tw] OR “neoplastic growth”[tw] OR “malignant growth”[tw] OR Hyperplasia[tw] OR Metaplasia[tw] OR “Apoptosis inhibition”[tw] OR Angiogenesis [tw] OR “heat shock protein”[tw] OR “extracellular matrix”[tw])		
4	((("etiology"[sh] OR "Causality"[mh] OR "biomarkers, tumor"[mh] OR "oncogene fusion"[mh] OR"tumor necrosis factors"[mh] OR "adverse-outcome-pathway*"[tiab] OR "biological-marker"[tiab] OR "biological-markers"[tiab] OR "biomarkers"[tiab] OR "biomarker"[tiab] OR "Biotransformation"[tiab] OR "etiology"[tiab] OR "Key Event*"[tiab] OR "Mechanism-of-action"[tiab] OR "Mechanisms-of-action"[tiab] OR "Mode-of-action"[tiab] OR "modes-of-action"[tiab] OR "Molecular-Initiating-Event*"[tiab] OR "neoplastic-cell-transform*"[tiab] OR "Phosphorylation"[tiab] OR "Toxicity-Pathway*"[tiab] OR "toxicokinetic*"[tiab] OR "toxic-pathway*"[tiab]) AND (neoplasms[mh] OR "angiogenesis inducing agents"[mh] OR "angiogenesis inducing agents"[nm] OR "antibodies, neoplasm"[mh] OR "antigens, neoplasm"[mh] OR carcinogens[mh] OR carcinogens[nm] OR "gene expression regulation"[mh] OR "genes, neoplasm"[mh] OR	3286350	RoC Other Mechanistic

Set	Search Terms	Retrieval	Concept Group
	"neoplasm proteins"[mh] OR "neoplastic processes"[mh])) OR ("tumor-inhibit*"[tiab] OR "tumor-promot*"[tiab] OR "tumour-inhibit*"[tiab] OR "tumour-promot*"[tiab] OR "Oncogenes"[tiab] OR "Oncogenesis"[tiab] OR "Oncogenic"[tiab] OR "pathogenesis"[tiab]))		
5	#1 AND (#2 OR #3 OR #4)	**504**	Chemical + (KC or Other Mech)
6	(drug[tiab] OR drugs[tiab] OR therap*[tiab] OR drug therapy[mh] OR acetylation[tiab] OR "ethylene vinyl acetate"[tiab] OR "polyethylene vinyl acetate"[tiab] OR "poly ethylene vinyl acetate"[tiab] OR "co vinyl acetate"[tiab] OR "poly vinyl acetate"[tw] OR "poly vinylacetate"[tw] OR "drug implants"[mh] OR "administration and dosage"[sh] OR delivery[ti] OR synthesis[tiab] OR chemistry[sh] OR "copolymer*"[ti] OR "polymer*"[ti] OR cataly*[ti])	**9865048**	unwanted concepts: drug delivery, copolymers, chemical synthesis
7	#5 NOT #6	**74**	Remove unwanted concepts

Table A17. PubMed Search Strategy for Acetaldehyde Metabolism

Search Terms	Retrieval	Concept
(("Acetaldehyde/metabolism"[Mh] OR "acetaldehyde metabolism"[tiab:~2]) AND (human*[tiab] OR humans[mh] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR animals[mh])) NOT (alcohol*[ti] OR ethanol[ti] OR "alcohol metabolism"[tiab:~1] OR "ethanol metabolism"[tiab:~1] OR alcohol[mh] OR "alcohol consumption"[tiab])	**599**	general acetaldehyde metabolism

Table A18. PubMed Search Strategy for Acetaldehyde + Vinyl Acetate

Search Terms	Retrieval	Concept
(("Acetaldehyde/metabolism"[Majr] OR ("acetaldehyde metabolism"[tiab:~1])) AND (human*[tiab] OR humans[mh] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR animals[mh])) AND "vinyl acetate"	**4**	Acetaldehyde + VA

Table A19. PubMed Search Strategy for Acetaldehyde + Cytochrome P450 or Monooxygenase

Search Terms	Retrieval	Concept
(("Acetaldehyde/metabolism"[Majr] OR ("acetaldehyde metabolism"[tiab:~1])) AND (human*[tiab] OR humans[mh] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR animals[mh])) AND ("cytochrome P450" OR CYP OR "mono oxygenase" OR monooxygenase)	**55**	acetaldehyde and CP450/mono oxygenase

Table A20. PubMed Search Strategy for Enzyme Polymorphisms

Search Terms	Retrieval	Concept
(carboxylesterase* OR "aldehyde dehydrogenase" OR AldDH[tiab] OR ALDH[tiab] OR ALDH1*[tiab] OR ALDH2[tiab]) AND polymorphism*	**1738**	Enzyme polymorphisms

APPENDIX B. OEHHA'S CALCULATION OF RISK ESTIMATES FOR TWO EPIDEMIOLOGICAL STUDIES

Risk estimates were not presented in Lewis and Rampala (2003) and Austin and Schnatter (1983) but could be calculated from data reported in these publications.

Lewis and Rampala (2003)

OEHHA calculated risk estimates from the logistic regression results presented in Lewis and Rampala (2003) for angiosarcoma of the liver. The logistic regression results are shown here in Table B1.

Table B1. Results of logistic regression analysis for vinyl acetate presented in Table 11 of Lewis and Rampala (2003)

Chemical	Coefficient	Standard error (SE)	SE %	*p* value
Vinyl acetate	–0.0009	0.0028	3.1111	0.7415

In a logistic regression model, the coefficients represent the log odds. Thus, the odds ratio (OR) can be calculated as e^(coefficient), and the confidence intervals (CI) can be calculated as e^(coefficient ± 1.96 * standard error [SE]). Inserting the data from Appendix Table B1 into these equations yields the following:

$$OR = e^{-0.0009} = 0.9991$$

$$\text{Lower CI} = e^{(-0.0009 - 1.96 * 0.0028)} = 0.9936$$

$$\text{Upper CI} = e^{(-0.0009 + 1.96 * 0.0028)} = 1.0046$$

Rounding the results of the above calculations results in an OR of 1.0 (95% CI, 0.994–1.005).

Austin and Schnatter (1983)

For Austin and Schnatter (1983), data from Table 8 of the publication, shown in Table B2, below, were used to calculate the ORs and 95% CIs for brain cancer. Table 8 was chosen since it accounts for a latency period of 15 years.

Table B2. Number of cases, controls and hourly controls ever exposed to vinyl acetate for 15 years or more prior to death, adapted from Table 8 of Austin and Schnatter (1983)

	All cases	Gliomas	Control 1	Control 2	Hourly control 1	Hourly control 2
Number of employees whose exposure status to vinyl acetate could be determined	10	9	33	29	29	27
Percentage of employees exposed to vinyl acetate	50%	55.6%	36.4%	37.9%	37.9%	37%

The information presented in Table B2 was used to calculate the numbers of cases and controls who were exposed and unexposed, as input to contingency tables. Contingency tables (e.g., Table B3) were then used to calculate ORs and 95% CIs as follows:

Table B3. Example of a contingency table

	Cases	Controls
Exposed	a	b
Unexposed	c	d

OR = ad/bc

95% CI = e^[ln(OR) ± 1.96 x √(1/a + 1/b + 1/c + 1/d)]

As an example, the OR and 95% CI calculations for all cases and "Control 1" are shown below.

Table B4. Contingency table for all cases and "Control 1"

	All cases	Control 1
Exposed	10*0.5 = 5	33*0.364 = 12
Unexposed	10*(1–0.5) = 5	33*(1–0.364) = 21

OR = (5*21)/(12*5) = 1.75

Lower CI = e^[ln(1.75) + 1.96 x √(1/5 + 1/12 + 1/5 + 1/21)] = 0.42

Upper CI = e^[ln(1.75) – 1.96 x √(1/5 + 1/12 + 1/5 + 1/21)] = 7.3

Thus, in this example the OR for all cases and “Control 1” is 1.75 (95% CI, 0.42–7.3). The ORs for the other control groups and for gliomas were calculated in a similar manner.