Evidence on the Carcinogenicity of Vinyl Acetate

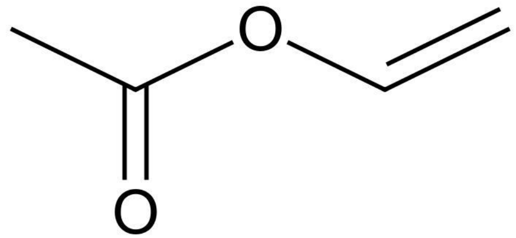
Carcinogen Identification Committee Meeting
December 19, 2024

Cancer Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment, CalEPA

Overview

- Introduction
- Epidemiologic studies
- Animal studies
- Mechanistic considerations
  - Pharmacokinetics and metabolism
  - Key characteristics (KCs) of carcinogens
- Similarities between vinyl acetate and acetaldehyde: carcinogenicity and genotoxicity

Vinyl Acetate



- A synthetic high production volume chemical
- Uses
  - Monomer to manufacture polymers (e.g., polyvinyl acetate) for a variety of applications
  - Food additives: vinyl acetate monomer or vinyl acetate-based polymers
- Occurrence and exposure
  - Detected in
    - Environment: air, water, soil and sediment
    - Consumer products: e.g., building materials, food packaging
  - Occupational exposure
  - General population may be exposed to low levels

Reviews by other health agencies

- IARC (1995): Group 2B carcinogen (possibly carcinogenic to humans)
  - Inadequate evidence in humans; limited evidence in experimental animals
  - Considerations:

    (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*.
- ECHA (2011): Category 2 carcinogen (suspected of causing cancer)

* Acetaldehyde is listed as a carcinogen under Proposition 65. IARC: Group 2B with sufficient evidence in experimental animals. NTP: reasonably anticipated to be a human carcinogen.

Epidemiological studies: vinyl acetate and cancer

- Few studies identified
- One study per cancer type
- All studies but one were in workers exposed occupationally
  - Co-exposures include: vinyl chloride, acrylonitrile, 1,3-butadiene, acrylamide, vinylidene chloride, benzene, ethylene oxide, acetaldehyde, styrene, trichloroethane
  - Some increased risks were observed but chance, bias, and confounding are possible

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Residential vinyl acetate & breast cancer: Heck et al. (2024)

- Prospective cohort of 48,665 women
- Exposure: residences geocoded to census tracts linked to the National Air Toxics Assessment (NATA)
- Outcome: linkage to CA Cancer Registry

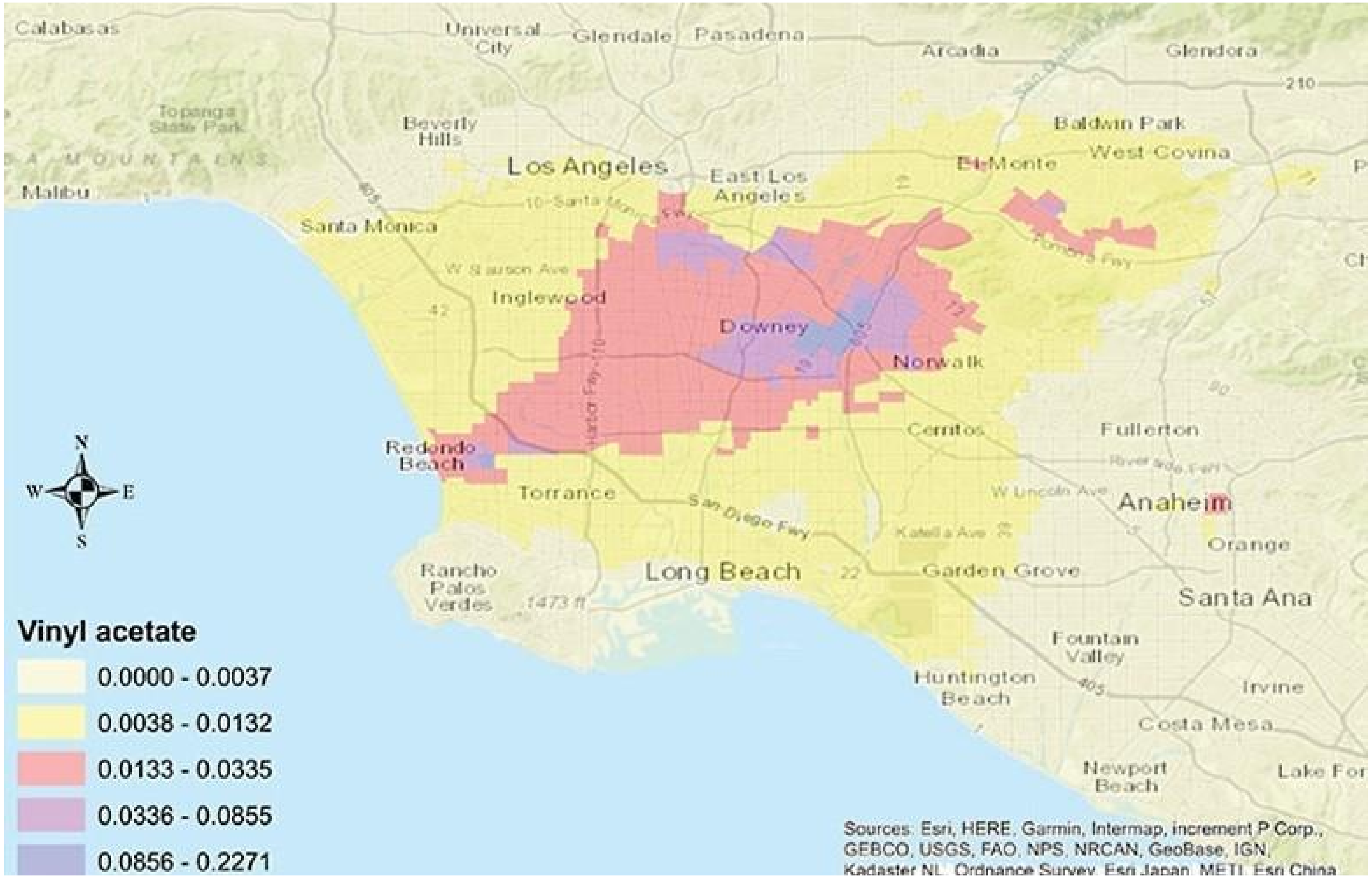
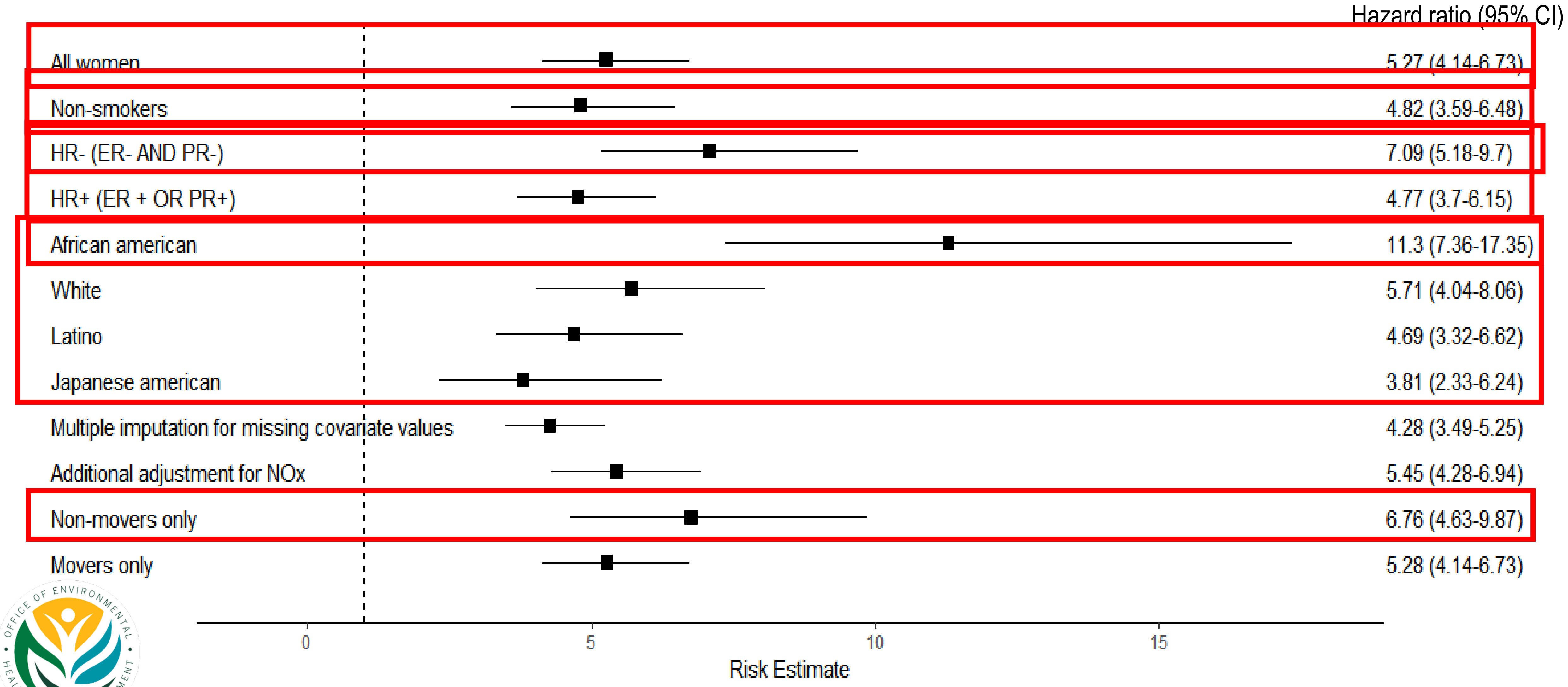


Figure 1. Exposure concentration of vinyl acetate reported in the greater Los Angeles area (Heck et al. 2024)

Residential vinyl acetate & breast cancer: Heck et al. (2024)



Residential vinyl acetate & breast cancer: Heck et al. (2024)

- Strengths
  - Large sample size
  - Prospective cohort
  - Multiethnic population
  - Detailed questionnaire that collected data on multiple covariates
  - Detailed residential histories
- Limitations
  - Air pollution estimates at the census tract level
  - Non-exhaustive list of chemicals
  - Missing potential earlier life exposures

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Carcinogenicity Studies in Animals

Animal Carcinogenicity Bioassays

Species	No. of studies	No. of strains	Routes
Rat	16	5	Inhalation (2 studies), Drinking water (14 studies)
Mouse	8	3	Inhalation (2 studies), Drinking water (6 studies)

Vinyl Acetate Animal Studies – Overview

Species	Route	Strain (Sex)	Concentrations (ppm)	Reference
Rat	Inhalation	Crl:CD(SD)BR (M, F)	0, 50, 200, 600	Bogdanffy et al. (1994a), Owen (1988)
	Drinking water	Fisher 344 (M, F)	0, 1000, 2500	Lijinsky and Reuber (1983), EPL (1982)
		F344/DuCrj (M, F)	0, 400, 2000, 10000	Umeda et al. (2004), JBRC (1995)
		SD F_0 (M, F); F_1(M, F)	0, 1000, 5000	Minardi et al. (2002)
		Wistar F_0 (M, F); F_1(M, F)	0, 1000, 5000	Belpoggi et al. (2002)
		Crl:CD(SD)BR F_1 (M, F)	0, 200, 1000, 5000	Bogdanffy et al. (1994b); Shaw (1988)
Mouse	Inhalation	Crl:CD-1(ICR)BR (M, F)	0, 50, 200, 600	Bogdanffy et al. (1994a), Owen (1988)
	Drinking water	Crj:BDF1 (M, F)	0, 400, 2000, 10000	Umeda et al. (2004), JBRC (1995)
		Swiss F_0 (M, F); F_1(M, F)	0, 1000, 5000	Maltoni et al. (1997)

Vinyl Acetate Animal Studies – Overview

Species	Route	Strain (Sex)	Concentrations (ppm)	Reference
Rat	Inhalation	**Crl:CD(SD)BR (M, F)**	0, 50, 200, 600	Bogdanffy et al. (1994a), Owen (1988)
	Drinking water	**Fisher 344** (M, **F**)	0, 1000, 2500	Lijinsky and Reuber (1983), EPL (1982)
		F344/DuCrj (M, F)	0, 400, 2000, 10000	Umeda et al. (2004), JBRC (1995)
		SD F_0 (M, F); F_1(M, F)	0, 1000, 5000	Minardi et al. (2002)
		Wistar F_0 (M, **F); F_1(M, F)**	0, 1000, 5000	Belpoggi et al. (2002)
		Crl:CD(SD)BR F_1 (M, F)	0, 200, 1000, 5000	Bogdanffy et al. (1994b); Shaw (1988)
Mouse	Inhalation	Crl:CD-1(ICR)BR (M, F)	0, 50, 200, 600	Bogdanffy et al. (1994a), Owen (1988)
	Drinking water	**Crj:BDF1 (M, F)**	0, 400, 2000, 10000	Umeda et al. (2004), JBRC (1995)
		Swiss F_0 (M, **F); F_1(M, F)**	0, 1000, 5000	Maltoni et al. (1997)

Vinyl Acetate Animal Studies – Before and After IARC 1995

Species	Route	Strain (Sex)	Concentrations (ppm)	Reference
Rat	Inhalation	**Crl:CD(SD)BR (M, F)**	0, 50, 200, 600	Bogdanffy et al. (1994a), Owen (1988)
	Drinking water	**Fisher 344** (M, **F**)	0, 1000, 2500	Lijinsky and Reuber (1983), EPL (1982)
		F344/DuCrj (M, F)	0, 400, 2000, 10000	Umeda et al. (2004), JBRC (1995)
		SD F_0 (M, F); F_1(M, F)	0, 1000, 5000	Minardi et al. (2002)
		Wistar F_0 (M, **F); F_1(M, F)**	0, 1000, 5000	Belpoggi et al. (2002)
		Crl:CD(SD)BR F_1 (M, F)	0, 200, 1000, 5000	Bogdanffy et al. (1994b); Shaw (1988)
Mouse	Inhalation	Crl:CD-1(ICR)BR (M, F)	0, 50, 200, 600	Bogdanffy et al. (1994a), Owen (1988)
	Drinking water	**Crj:BDF1 (M, F)**	0, 400, 2000, 10000	Umeda et al. (2004), JBRC (1995)
		Swiss F_0 (M, **F); F_1(M, F)**	0, 1000, 5000	Maltoni et al. (1997)

Tumor Incidence Data

- Tumor site/type, test concentrations, exact trend test values
- Significant increase (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ by Fisher pairwise comparison)
- Dose-related trend ($p < 0.05$)
- Rare tumor (r)

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Rat Studies

Tumor incidence: 104-week inhalation study in male Crl:CD(SD)BR rats

(Bogdanffy et al. 1994a; Owen 1988)

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

(r), rare tumor; week of first nasal tumor occurrence: 103 weeks

**, $p < 0.01$ by Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week inhalation study in female Crl:CD(SD)BR rats

(Bogdanffy et al. 1994a; Owen 1988)

Tumor site	Tumor type	Administered concentration (ppm)				Trend test *p*-value
		0	50	200	600	
Nasal cavity	Squamous cell carcinoma (r)	0/34	0/37	0/41	4/46	< 0.01

(r), rare tumor; week of first nasal tumor occurrence: 95 weeks

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Tumor incidence: 100-week drinking water study in female Fischer 344 rats (EPL 1982; Lijinsky and Reuber 1983)

Tumor site	Tumor Type	Administered concentration (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	Adenoma	6/17	8/19	12/18	< 0.05

(r), rare tumor; *, $p < 0.05$, **, $p < 0.01$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water study in male F344/DuCrj rats (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration (ppm)				Trend test *p*-value
		0	400	2000	10000	
Oral cavity (and 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**	< 0.001
Testes	Interstitial cell tumor	42/50	40/50	44/50	47/50	< 0.05

(r), rare tumor; *, $p < 0.05$, **, $p < 0.01$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water study in female F344/DuCrj rats (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration (ppm)				Trend test *p*-value
		0	400	2000	10000	
Oral cavity (and 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	Adenocarcinoma	0/50	0/50	0/50	3/50	< 0.05

(r), rare tumor; *, $p < 0.05$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water studies in male F_0 and F_1 Sprague-Dawley rats (Minardi et al. 2002)

Study	Tumor site	Tumor type	Administered concentration (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***	< 0.001
	Forestomach	Squamous cell carcinoma (r)	0/107	6/83**	7/53***	< 0.01
	Pancreas	Exocrine adenoma (r)	0/107	5/83*	1/53	NS

(r), rare tumor; *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water studies in female F_0 and F_1 Sprague-Dawley rats (Minardi et al. 2002)

Study	Tumor site	Tumor type	Administered concentration (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***	< 0.001
	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	Pheochromoblastoma	1/99	6/87*	3/57	NS

(r), rare tumor; *, $p < 0.05$, ***, $p < 0.001$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

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Tumor incidence: 104-week drinking water study in male F_1 Wistar rats

(Belpoggi et al. 2002)

Tumor site	Tumor type	Administered concentration (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

*, $p < 0.05$, **, $p < 0.01$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water study in female F_0 Wistar rats

(Belpoggi et al. 2002)

	Tumor site	Tumor type	Administered concentration (ppm)			Trend test *p*-value
			0	1000	5000	
F_0	**Hemolympho-reticular tissues**	Lymphoma and leukemia	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

*, $p < 0.05$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water study in female F_1 Wistar rats (Belpoggi et al. 2002)

	Tumor site	Tumor type	Administered concentration (ppm)			Trend test
			0	1000	5000	*p*-value
F_1	Hemolympho-reticular tissues	Lymphoma and leukemia	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

*, $p < 0.05$, **, $p < 0.01$, Fisher pairwise comparison

104-week drinking water studies in male and female F_1 Crl:CD(SD)BR rats

(Bogdanffy et al. 1994b; Shaw 1988)

- F_1 animals (60 rats/group) were exposed to VA throughout all life stages (preconception, *in utero*, and continuing after birth) until 104 weeks of age.
- Administered concentrations are 0, 200, 1000, 5000 ppm to F_0 and F_1.
- In F_1 males, two rare squamous carcinomas of the oral cavity were observed in the 5000 ppm group.
- In F_1 females, no treatment-related tumor findings were observed.

Mouse Studies

Tumor incidence: 104-week drinking water study in male Crj:BDF1 mice

(JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration (ppm)				Trend test *p*-value
		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***	< 0.001
	Combined (r)	0/50	0/50	0/50	16/50***	< 0.001
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**	< 0.001
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**	< 0.001

(r), rare tumor; *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 104-week drinking water study in female Crj:BDF1 mice (JBRC 1995; Umeda et al. 2004)

Tumor site	Tumor type	Administered concentration (ppm)				Trend test *p*-value
		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***	< 0.001
	Combined (r)	0/50	0/50	0/50	18/50***	< 0.001
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

(r), rare tumor; *, $p < 0.05$, ***, $p < 0.001$, Fisher pairwise comparison; NS, not significant ($p \geq 0.05$)

Tumor incidence: 78-week drinking water study in male F_1 Swiss mice (Maltoni et al. 1997)

Tumor site	Tumor type	Administered concentration (ppm)			Trend test *p*-value
		0	1000	5000	
Oral cavity	Squamous cell carcinoma	0/38	0/37	10/49**	< 0.001
Tongue	Squamous cell carcinoma	1/38	0/37	7/49	< 0.01
Esophagus	Squamous cell carcinoma	0/38	0/37	12/49***	< 0.001
Forestomach	Acanthoma	0/38	1/37	8/49**	< 0.01

**, $p < 0.01$, ***, $p < 0.001$, Fisher pairwise comparison

Tumor incidence: 78-week drinking water studies in female F_0 and F_1 Swiss mice (Maltoni et al. 1997)

	Tumor site	Tumor type	Administered concentration (ppm)			Trend test *p*-value
			0	1000	5000	
F_0	**Esophagus**	Squamous cell carcinoma	0/37	0/37	6/37*	0.001
	Forestomach	Acanthoma	0/37	0/37	5/37*	< 0.01
		Squamous cell carcinoma	0/37	0/37	3/37	< 0.05

*, $p < 0.05$, Fisher pairwise comparison

Tumor incidence: 78-week drinking water studies in female F_0 and F_1 Swiss mice (Maltoni et al. 1997, continued)

	Tumor site	Tumor type	Administered concentration (ppm)			Trend test *p*-value
			0	1000	5000	
F_1	**Oral cavity**	Squamous cell carcinoma	0/48	0/44	9/48**	< 0.001
	Tongue	Squamous cell carcinoma	0/48	0/44	12/48***	< 0.001
	Esophagus	Acanthoma	0/48	0/44	3/48	< 0.05
		Squamous cell carcinoma	0/48	0/44	18/48***	< 0.001
	Forestomach	Acanthoma	0/48	0/44	11/48***	< 0.001
		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

**, $p < 0.01$, ***, $p < 0.001$, Fisher pairwise comparison

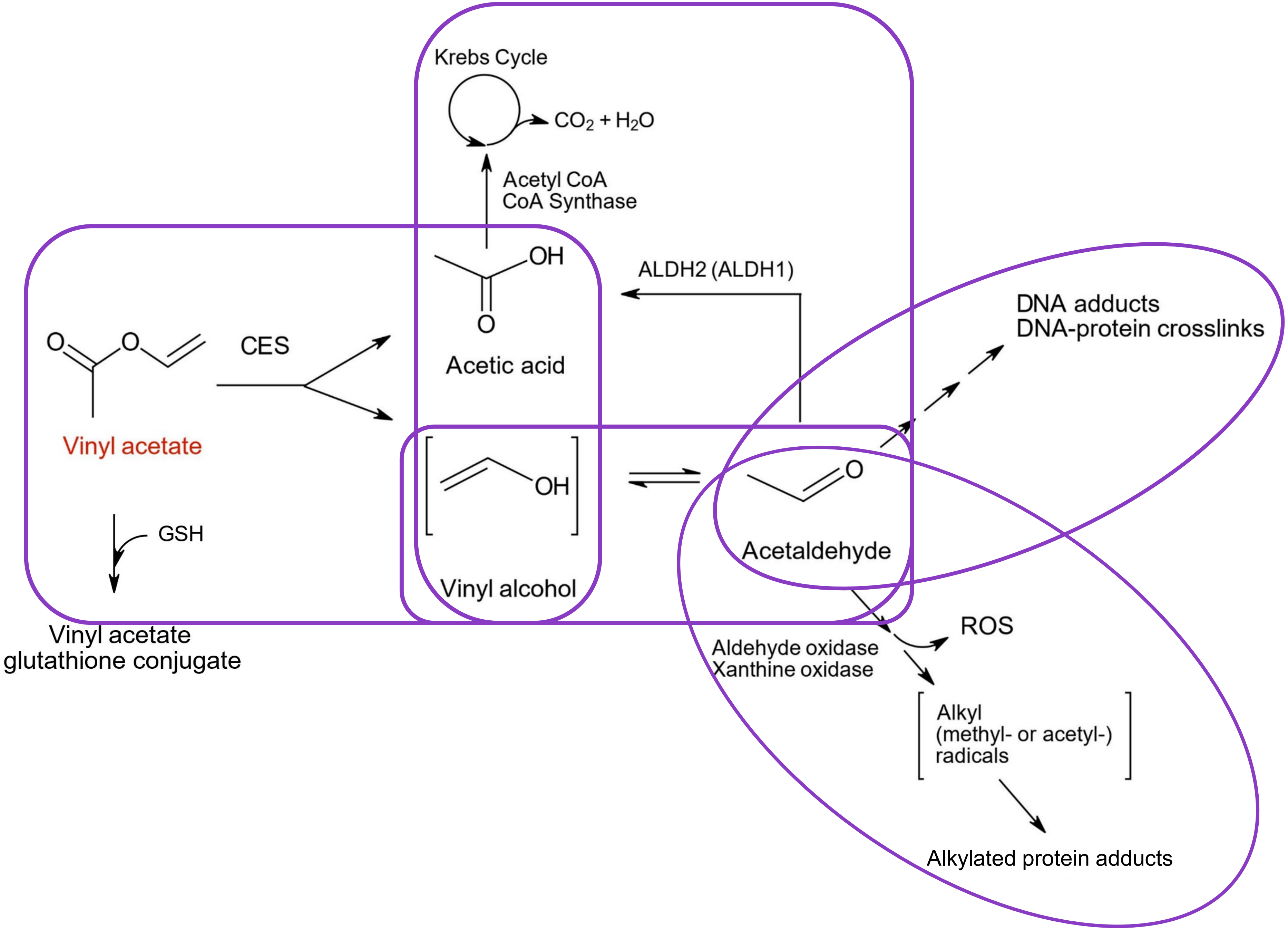
Summary of Animal Tumor Findings

M, male; F, female; ^{r}, Rare

System	Tumor site	Crl:CD(SD)BR rat	SD rat	Fischer 344 rat	F344/DuCrj rat	Wistar rat	Swiss mouse	Crj:BDF1 mouse
Respiratory	Nasal cavity	**M^r**, F^r						
	Larynx	F^r						**M^r**
	Other sites					M (Pharynx)	F (Lung)	
Digestive	Oral cavity		**M, F**		**M^r, F^r**	**M, F**	**M, F**	**M^r, F^r**
	Tongue		F^r			**F**	M, **F**	
	Esophagus					M, **F**	**M, F**	**M^r**
	Forestomach		**M^r, F^r**			M, F	**M, F**	**M^r**, F^r
	Liver			**F**				
	Pancreas		**M^r**			**M**		
Endocrine	Adrenal gland		**F**			**M, F**		
	Thyroid gland			**F**	**F**			
	Pituitary gland			**F**				
Reproductive	Uterus			**F^r**		**F**	**F**	
	Mammary gland				F		F	
	Testes				**M**			
Auditory	Zymbal Gland						**F**	
Immune	Hemolymphoreticular					**F**		**F**

Pharmacokinetics and Metabolism

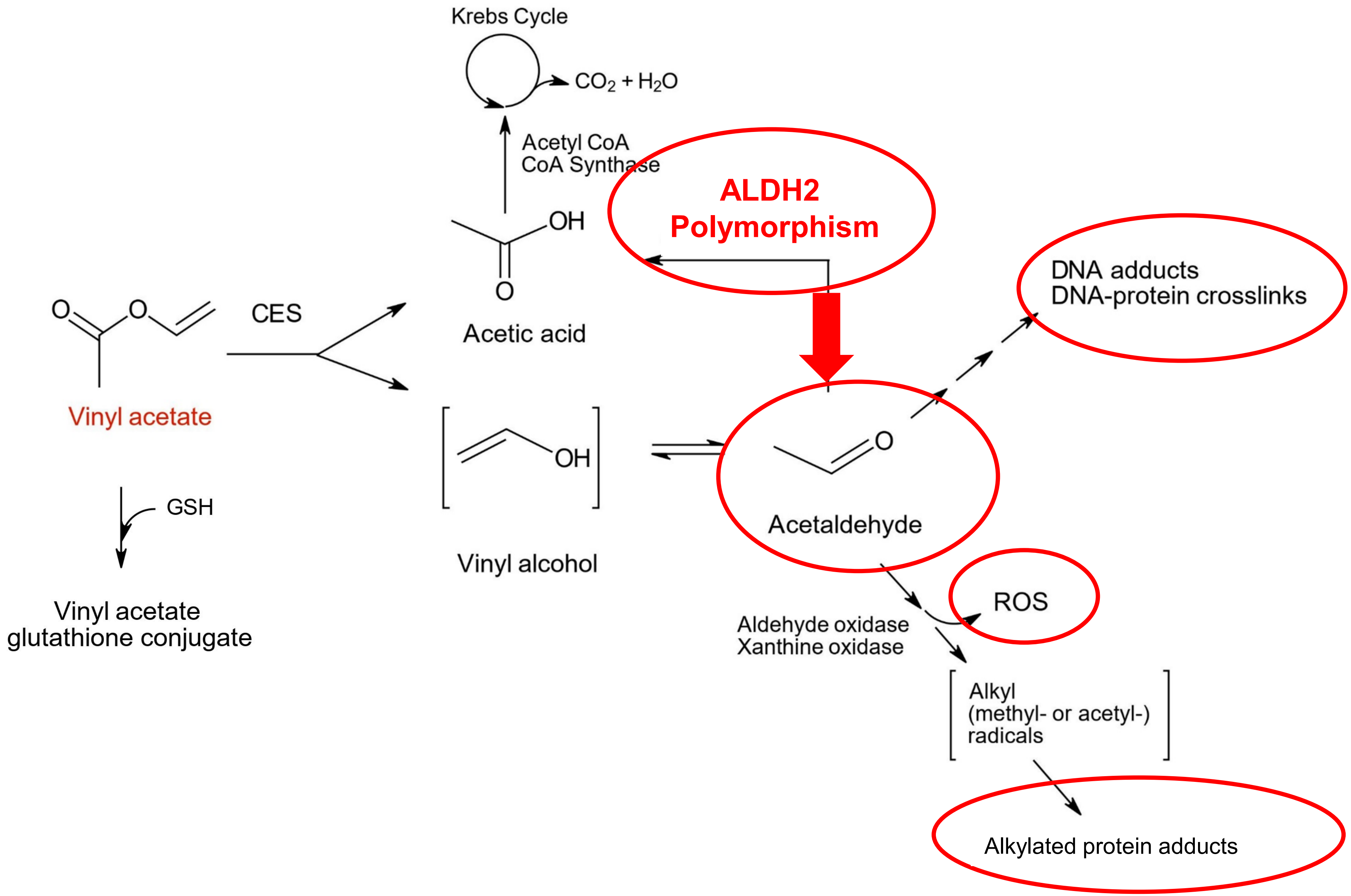
- Fast absorption & distribution throughout the body
- Rapid excretion within 24 hours: expired air, urine and feces
- Two key enzymes:
  - Carboxylesterases (CES):
    - **Vinyl acetate →** acetic acid and **acetaldehyde (genotoxic carcinogen)**
  - Aldehyde dehydrogenase 2 (ALDH2)
    - **Acetaldehyde →** acetic acid
- Other metabolic reactions



Krebs Cycle
$CO_2 + H_2O$
Acetyl CoA
CoA Synthase
OH
O
Acetic acid
ALDH2 (ALDH1)
DNA adducts
DNA-protein crosslinks
O
O
CES
Vinyl acetate
OH
O
Acetaldehyde
GSH
Vinyl alcohol
Vinyl acetate
glutathione conjugate
ROS
Aldehyde oxidase
Xanthine oxidase
Alkyl
(methyl- or acetyl-)
radicals
Alkylated protein adducts

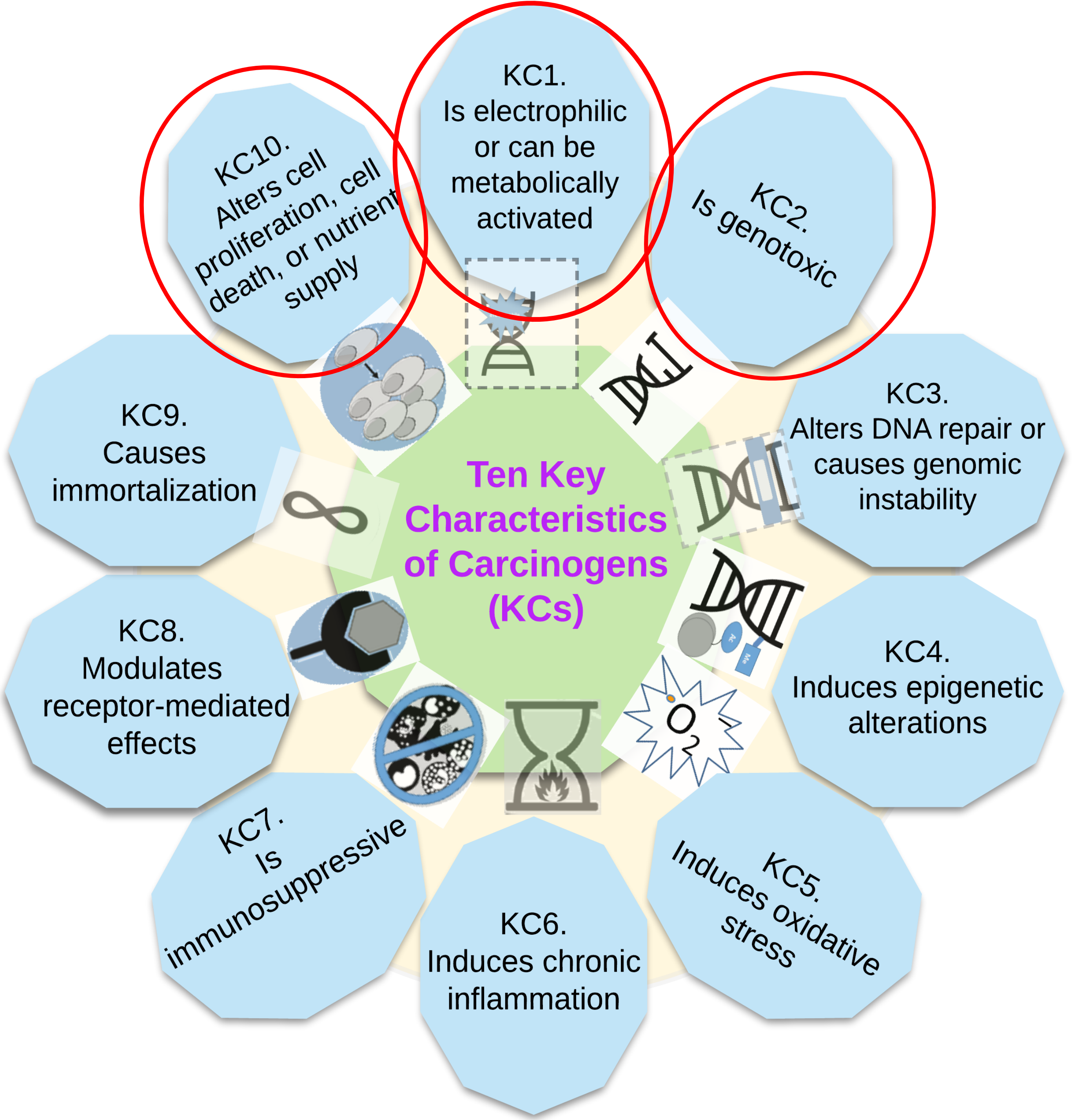
ALDH2 rs671 Polymorphism

- Partial or complete loss of function
  - ALDH2 *1/*1, full activity
  - ALDH2 *1/*2, intermediate activity
  - ALDH2 *2/*2, no activity
    - “Alcohol flushing syndrome”
- ALDH2 *2 is common in East Asian populations – Up to 40% heterozygous ALDH2 *1/*2
  - 5–10% being homozygous ALDH2 *2/*2
- Reduced or non-functioning ALDH2 variants can result in significant build-up of acetaldehyde
  - Estimated 1 million people in California may be affected



Krebs Cycle
$CO_2 + H_2O$
Acetyl CoA
CoA Synthase
ALDH2
Polymorphism
OH
O
Acetic acid
CES
O
O
Vinyl acetate
GSH
Vinyl acetate
glutathione conjugate
OH
Vinyl alcohol
O
Acetaldehyde
DNA adducts
DNA-protein crosslinks
ROS
Aldehyde oxidase
Xanthine oxidase
Alkyl
(methyl- or acetyl-)
radicals
Alkylated protein adducts

Key Characteristics of Carcinogens



Images of the KCs are adapted from Guyton et al. (2018) & Smith et al. (2020) with modifications. See also Preamble to the IARC monographs (IARC 2019).

KC 1: Is Electrophilic or Can Be Metabolically Activated

- Formation of DNA adducts *in vivo* in rats treated with vinyl acetate: $[^{13}C_2]$-N^2-Ethyl-dG in nasal respiratory and olfactory epithelia, peripheral blood mononuclear cells
    - No adducts were observed in liver, brain, or bone marrow
- Electrophilic and reactive metabolite: Acetaldehyde
    - Acetaldehyde binds directly to DNA, forming
        - N^2-Ethyl-dG
        - 1, N^2-propano-dG
        - NεG

Section 5.2.1

KC 2: Is Genotoxic

Chromosomal effects

- ↑ in chromosomal aberrations in lymphocytes of polyvinyl acetate manufacturing workers
- ↑ in micronuclei, chromosomal aberrations, and sister chromatid exchanges in *in vivo* animal studies and human *in vitro* studies
- ↑ in sister chromatid exchanges in animal *in vitro* studies

DNA damage

- ↑ DNA adduct formation in nasal epithelial and peripheral blood mononuclear cells in *in vivo* animal studies
- ↑ DNA-crosslinks in human leucocytes *in vitro*
- ↑ DNA-protein crosslinks in rat nasal epithelial cells *in vitro* and plasmid DNA and calf thymus histones with incubated rat liver microsomes

KC 2: Is Genotoxic (continued)

Mutations

- ↑ in human TK6 lymphoblastoid cells *in vitro* at *TK* locus, but not *HPRT* locus
- ↑ in mouse lymphoma cells *in vitro* at *TK* locus with and without S9
- No mutagenic activity was observed in tests conducted in multiple *Salmonella typhimurium* strains or two *E. coli* strains

KC 10: Alters Cell Proliferation, Cell Death, or Nutrient Supply

- ↑ Cell Proliferation
  - Male rats: nasal cavity epithelium, nasal olfactory epithelium, and oral cavity maxillary mucosa
  - Male mice: basal cells of the mandibular oral cavity mucosa
- ↑ Hyperplasia
  - Male and female rats: basal cell hyperplasia of the nose
  - Female rats: thyroid gland C-cell hyperplasia, hyperplasia of the esophagus and stomach
  - Male and female mice: tracheal epithelial hyperplasia, submucosal gland hyperplasia, basal and squamous cell hyperplasia in the oral cavity and esophagus
- ↑ Dysplasia
  - Male and female F_0 mice: squamous cell dysplasia of the esophagus
  - Female F_1 mice: squamous cell dysplasia of the tongue, esophagus, and Zymbal gland

Similarities between Vinyl Acetate and Acetaldehyde: Carcinogenicity and Genotoxicity

Shared Tumor Findings

	Vinyl Acetate	Acetaldehyde
Inhalation	• **Nasal tumors in rats** • Laryngeal tumors in rats	• **Nasal tumors in rats** • Laryngeal tumors in hamsters
Drinking water	• **Hemolymphoreticular cancer in rats (leukemia and lymphoma combined)** • **Pancreatic tumors in rats (islet cell adenoma and exocrine adenoma)** • **Mammary gland tumors in rats (adenocarcinoma) and mice (liposarcoma)** • And many more sites	• **Hemolymphoreticular cancer in rats (leukemia and lymphoma combined)** • **Pancreatic tumors in rats (islet cell adenoma)** • **Mammary gland tumors in rats (benign fibroma or fibroadenoma)** • Nasal cavity tumors in rats (carcinoma) • Bone tumors in rats (osteosarcoma)

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Shared Genotoxic Effects between Vinyl Acetate and Acetaldehyde

- Micronuclei, chromosomal aberrations, and sister chromatid exchanges in rodents *in vivo* and human and rodent cells *in vitro*
- Form N2-Ethyl-dG DNA adducts and DNA crosslinks
- *TK* locus mutations in human and mouse cells *in vitro*