Proposition 65

Ethoprop

A chemical listed “as causing cancer” by the authoritative bodies mechanism and under review by the Carcinogen Identification Committee

September 2026

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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PREFACE

This document presents evidence relevant to the evaluation of the carcinogenicity of ethoprop.

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 implementation of 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 US Environmental Protection Agency (US EPA) is a designated "authoritative body" whose formal identification of carcinogens serves as the basis for listing chemicals under Proposition 65. OEHHA listed ethoprop as a carcinogen under Proposition 65 on February 27, 2001, based upon its classification by US EPA (US EPA 1997a)[2] as a "likely" human carcinogen. In 2020, US EPA revised the classification of ethoprop to "Suggestive Evidence of Carcinogenic Potential" (US EPA 2020).[3] This updated classification no longer meets the Proposition 65 regulatory criteria for listing under the authoritative body mechanism.

Ethoprop is no longer formally identified by US EPA as causing cancer and is being referred to the CIC, the state's qualified experts for carcinogenicity determinations under Proposition 65. The CIC will recommend whether ethoprop should continue to be included on the list of chemicals known to the state to cause cancer. To make such a recommendation, the CIC determines whether the 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 is scheduled to meet on November 17, 2026. OEHHA is providing this document to the CIC to assist the Committee in its deliberations on whether or not

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code 25249.5 *et seq*., commonly referred to as Proposition 65.

[2] US Environmental Protection Agency (US EPA, 1997a). Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Ethoprop. Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. September 25, 1997.

[3] US Environmental Protection Agency (US EPA, 2020). Cancer Assessment Document. Re-Evaluation of the Carcinogenic Potential of Ethoprop. PC Code 041101. Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. March 16, 2020.

ethoprop should remain 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.

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LIST OF ABBREVIATIONS

Abbreviation	Full name
µg	Micrograms
µg/L	Micrograms per liter
µg/m^3	Micrograms per cubic meter
µM	Micromolar
A	Absorption
AChE	Acetylcholinesterase
AhR	Aryl hydrocarbon receptor
AR	Androgen receptor
BW	Body weight
CalPIQ	California Pesticide Illness Query
CAR	Constitutive androstane receptor
CAs	Chromosomal aberrations
CAT	Catalase
CIC	Carcinogen Identification Committee
CLP	Classifying, labeling, and packaging
CompTox Chemical Dashboard	Computational Toxicology Chemicals Dashboard
CYP	Cytochrome P-450 monooxygenases
DNA	Deoxyribonucleic acid
D	Distribution
E	Elimination
EC	Emulsifiable concentrate
ECHA	European Chemicals Agency
EDSP	Endocrine Disruptor Screening Program
ER	Estrogen receptor
F_0	Parental/breeder animals
F_1	Offspring
F344	Fischer 344
g	Grams
GenRA	Generalized Read-Across
g/mol	Grams per mole
GPx	Glutathione peroxidase

Abbreviation	Full name
GR	Glutathione reductase
GSH	Glutathione
GSI	Gonado-somatic index
GSRI	Gulf South Research Institute
GSSG	Glutathione disulfide
GST	Glutathione-S-transferase
HAWC	Health Assessment Workspace Collaborative
HED	Health Effects Division
HLL	Hind-limb length
hpf	Hours post fertilization
HPT	Hypothalamus-pituitary-thyroid
IARC	International Agency for Research on Cancer
IL	Interleukins
i.v.	Intravenous
KCs	Key characteristics
kg	Kilograms
Koa	Octanol-air partition coefficient
Kow	Octanol-water partition coefficient
LABC	Levator ani-bulbocavernosus
LD_{50}	Median lethal dose
LPO	Lipid peroxidation
M	Metabolism
MDA	Malondialdehyde
mg	Milligrams
mg/kg	Milligrams per kilogram
mg/kg-bw	Milligrams per kilogram body weight
mg/kg/day	Milligrams per kilogram per day
mg/L	Milligrams per liter
mL	Milliliter
mM	Millimolar
MN	Micronuclei
MOA	Mode of action
mol/L	Moles per liter
NA	Not applicable

Abbreviation	Full name
NC	Not considered
NF	Nieuwkoop-Faber
ng/m^3	Nanograms per cubic meter
NIOSH	National Institute of Occupational Safety and Health
NO	Nitric oxide
NOEL	No observed effect level
NS	Not significant
NTP	National Toxicology Program
ºC	Degrees Celsius
OEHHA	Office of Environmental Health Hazard Assessment
PECO	Populations, exposures, comparators, and outcomes
PM_{10}	Particulate matter with a diameter less than 10 micrometers
PND	Postnatal day
PPAR	Peroxisome proliferator-activated receptor
ppb	Parts per billion
PPE	Personal protective equipment
ppm	Parts per million
PWG	Pathology Working Group
RNS	Reactive nitrogen species
RoC	Report on Carcinogens
ROS	Reactive oxygen species
SD	Sprague-Dawley
SOD	Superoxide dismutase
SPF	Specific pathogen free
SURF	Surface Water Database
SVL	Snout-vent length
T4	Thyroxine
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
TRI	Toxics Release Inventory
TSH	Thyroid stimulating hormone
UDS	Unscheduled DNA synthesis
US	United States
USDA	United States Department of Agriculture

Abbreviation	Full name
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
US GAO	United States General Accounting Office
VO	Vaginal opening
VTG	Vitellogenin

SUMMARY

Ethoprop is a volatile synthetic organophosphate pesticide used as an insecticide, nematicide, and fungicide. Ethoprop is registered as a pesticide under the US Environmental Protection Agency (US EPA) and is also registered with the California Department of Pesticide Regulation (CDPR). Due to its acute toxicity, ethoprop is a restricted use pesticide, and it is not available for purchase or use by the general public.

About 13,000 pounds (lbs) of ethoprop were used across ten counties in California in 2023 on various agricultural commodities, including sweet potato and potato (CDPR 2026d). US EPA set a tolerance level of 0.02 parts per million (ppm) for ethoprop for several raw agricultural commodities (e.g., sweet potato, potato, bean, corn, hop, mint and banana) (CFR 2026) and based on multi-year monitoring data from the US Department of Agriculture (USDA) and CDPR the tolerance level has rarely been exceeded. There is no residential use of ethoprop. People may be exposed to ethoprop via the dermal (a major route for workers), inhalation, and ingestion routes.

Ethoprop was listed as known to the State of California to cause cancer under Proposition 65 on February 27, 2001, through the authoritative bodies listing mechanism. The Proposition 65 listing was based on the US EPA classification of ethoprop as a “likely” human carcinogen (US EPA 1997a). In 2020, US EPA reclassified ethoprop as “Suggestive Evidence of Carcinogenic Potential” (US EPA 2020).

Ethoprop is no longer formally identified by US EPA as “likely” causing cancer and is being referred to the Carcinogen Identification Committee (CIC), the state’s qualified experts for carcinogenicity determinations under Proposition 65. The Office of Environmental Health Hazard Assessment (OEHHA) has prepared this document to provide the CIC with information relevant to the assessment of the evidence of carcinogenicity of ethoprop.

Reviews by Other Health Agencies

Ethoprop has not been classified with regard to carcinogenicity by the International Agency for Research on Cancer (IARC), 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 2018, the European Food Safety Authority (EFSA 2018) classified ethoprop as a Category 2 carcinogen (“suspected of causing cancer”).

Systematic Literature Review Approach

OEHHA systematically conducted literature searches on the carcinogenicity of ethoprop. Literature searches on the carcinogenicity of ethoprop were initiated in October 2025 and last updated in August 2026. 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. Pesticide registrant studies were identified through other health agency reports and obtained on a basis of confidentiality. Literature searches were supplemented with a public data call-in period from December 19, 2025, to February 2, 2026; no submissions were received. An overview of the systematic literature review approach is presented in Section 2, and detailed information, including populations, exposures, comparators, and outcomes (PECO) criteria and descriptions of potentially relevant supplemental materials used for screening are provided in Appendix A.

Carcinogenicity Studies in Humans

No cancer epidemiological studies on the effects of human exposure to ethoprop were identified.

Carcinogenicity Studies in Animals

Dietary studies of ethoprop have been conducted in male and female Sprague-Dawley (SD) derived Crl:CD®(SD)BR VAF/Plus rats, Fischer 344 (F344) rats, and B6C3F_1 mice.

Statistically significant tumor findings were observed in multiple studies in rats and in one study in mice. Rare endometrial adenomas and adenocarcinomas were observed in female F344 rats exposed throughout the lifespan (parental exposure preconception, maternal exposure *in utero* and during lactation, direct exposure from weaning to 112 weeks of age). These statistically significant tumor findings are summarized here by organ and tumor type:

Adrenal gland

- Malignant pheochromocytoma
    - Male SD rats (1 ppm)

Thyroid gland

- C-cell adenoma
  - Male F344 rats (196 ppm [one study] and by trend [two studies])
- C-cell carcinoma
  - Male SD rats (by trend)
  - Male F344 rats (by trend)
- C-cell adenoma and carcinoma (combined)
  - Male SD rats (by trend)
  - Male F344 rats (100 ppm and by trend)

- Follicular cell adenoma
  - Male SD rats (400 ppm)

Uterus

- Endometrial adenoma and adenocarcinoma (combined) (rare)
  - Female F344 rats (by trend)

- Endometrial stromal polyp
  - Female SD rats (400 ppm and by trend)
- Endometrial polyp
  - Female F344 rats (98 and 196 ppm and by trend)
- Endometrial and stromal polyp (combined)
  - Female F344 rats (196 ppm and by trend)

Liver

- Hepatocellular adenoma
  - Male F344 rats (by trend)
- Hepatocellular carcinoma
  - Female B6C3F_1 mice (by trend)
- Hepatocellular adenoma and carcinoma (combined)
  - Male F344 rats (by trend)

Mechanistic Considerations and Other Relevant Data

Pharmacokinetics and metabolism

Data relevant to the absorption, distribution, metabolism, and elimination (ADME) of ethoprop in humans are available from one study in agricultural applicators and one unpublished *in vitro* study of excised human skin. Data are also available from *in vivo*

and *in vitro* studies conducted in animals. Specifically, studies have been conducted *in vivo* in rats and zebrafish and *in vitro* with rat and rabbit microsomes and mouse, rat, and rabbit skin.

Ethoprop appears to be readily absorbed and rapidly metabolized in occupationally exposed humans. It is also readily absorbed in rats and mice exposed by the oral route and in zebrafish embryos incubated in the presence of ethoprop. Ethoprop can also be absorbed through the skin, as demonstrated in *in vitro* studies of excised human, rat, mouse, and rabbit skin. Once absorbed, ethoprop enters the bloodstream, is distributed throughout the body, and rapidly metabolized. Ethoprop is metabolized primarily through de-propylation, with O-de-ethylation also occurring. Overall, the major metabolites of ethoprop are shared across rats and zebrafish, and detection of metabolite O-ethyl S-propyl phosphorothioate in human urine suggests similar metabolism occurs in humans as in rats.

Ethoprop does not accumulate in the body. Ethoprop is largely excreted in urine; feces and expired air are secondary routes of elimination.

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 ethoprop. Evidence related to four of the KCs (KC2, KC5, KC6 and KC8) was identified for ethoprop, and this evidence is briefly summarized here. See Section 5.2 for more detailed summaries of the data relevant to these KCs.

KC2. Is genotoxic

Ethoprop has been tested *in vivo* for chromosomal effects in mice, rats and tilapia and for mutagenicity in rats. *In vitro* tests with ethoprop include tests for chromosome aberrations (CAs) in Chinese hamster ovary (CHO) cells, DNA damage tests in carp cells and rat hepatocytes, and mutagenicity tests in mouse and CHO cells. Ethoprop was also tested for mutagenicity in plant and bacterial systems.

Overall, chromosomal effects, DNA damage, and mutagenicity were observed in studies of ethoprop conducted *in vivo* and *in vitro*. Increases in chromosomal aberrations were observed in the bone marrow of male Swiss albino mice in two studies, but not in one study in SD rats. Increases in micronuclei and 8-OHdG levels were observed in fish and an increase in DNA fragmentation was observed in brain tissue of mice exposed *in vivo*. Dominant lethal mutations were observed in one study in SD rats, but not in another in

CD (SD) rats. CAs and sister chromatid exchanges (SCEs) were increased in CHO cells exposed to ethoprop with S9 rat liver activation. DNA double strand breaks were increased in fish cells *in vitro*, but no evidence of unscheduled DNA synthesis was observed in rat hepatocytes exposed *in vitro*. Reverse mutations were increased in ethoprop-exposed corn, while no evidence of mutagenicity was observed in studies conducted in mouse lymphoma cells, CHO cells, *Salmonella typhimurium*, or *S. cerevisiae.*

KC5. Induces oxidative stress

OEHHA identified studies that assessed the induction of oxidative stress in ethoprop-exposed rats and fish *in vivo* and rats *in vitro*. Overall, evidence for ethoprop-induced oxidative stress was generally consistent both across the multiple biomarkers measured within individual studies, and across studies that assessed specific biomarkers, such as oxidative damage to DNA (one study), production of reactive oxygen or nitrogen species (ROS, RNS) (two studies), markers of lipid peroxidation (LPO) (four studies reported increases; two reported no changes), decreased reduced glutathione (GSH) (one study), and changes in antioxidant enzyme activity (three studies; two additional studies reported no changes). In the one study that assessed oxidative damage to DNA, increased liver 8-OHdG and LPO levels were observed in Nile tilapia, along with changes in antioxidant enzyme activity. In the two studies that assessed production of reactive oxygen or nitrogen species, increased reactive nitrogen species (nitric oxide) and malondialdehyde (MDA) levels, decreases in GSH, and changes in antioxidant enzyme activity were observed in brain tissues of ethoprop-exposed male rats, and increased ROS and MDA levels and changes in antioxidant enzyme activity were observed in zebrafish embryos. The fourth study to observe an increase in MDA levels was conducted in rat hepatocytes, while the two other studies assessing LPO, conducted in fish (adult tetras and gar larvae), reported no changes in either LPO or antioxidant enzyme activity.

KC6 Induces chronic inflammation

Ethoprop has been tested in one study with endpoints related to chronic inflammation; however, it is not a chronic study. In zebrafish embryos ethoprop exposure increased gene expression of tumor necrosis factor-alpha (Tnf-α) and interleukin-1 beta (IL-1β).

KC8 Modulates receptor-mediated effects

Data for ethoprop relevant to KC8 were available from testing performed as part of the US EPA's Endocrine Disruptor Screening Program (EDSP) Tier I screening battery, which consists of 11 assays. Data from this screening battery indicate that ethoprop exhibited anti-androgenic activity *in vivo* in the Hershberger assay in male rats, the

pubertal assay in male rats, and in male fathead minnows. Ethoprop also exhibited activity suggestive of effects on the hypothalamus-pituitary-thyroid axis in pubertal male rats. Other effects of ethoprop included increased estrogen synthesis *in vitro* in a human cell line and reproductive effects in female fathead minnows. Ethoprop tested negative or the findings were equivocal for other outcomes assessed.

Structure activity considerations

SAR assessment provided limited insight into the carcinogenicity of ethoprop. One structurally related organophosphate pesticide, tribufos, was identified for comparison with ethoprop. In mice, exposure to tribufos caused liver tumors and rare small intestine tumors in males and lung tumors in females. By comparison, ethoprop increased the incidence of adrenal gland tumors, thyroid C-cell tumors, thyroid follicular cell tumors, and liver tumors in male rats, rare uterine endometrial tumors and other types of uterine tumors in female rats, and liver tumors in female mice.

1. INTRODUCTION

This document summarizes the evidence of carcinogenicity for ethoprop, a pesticide that acts as an insecticide, nematicide, and fungicide (US EPA 1997a, 2020).

Ethoprop was listed as known to the State of California to cause cancer under Proposition 65 on February 27, 2001, through the authoritative bodies listing mechanism. The Proposition 65 listing was based on the US Environmental Protection Agency (US EPA) classification of ethoprop as a "likely" human carcinogen (US EPA 1997a). In 2020, US EPA reclassified ethoprop as "Suggestive Evidence of Carcinogenic Potential" (US EPA 2020). This updated classification no longer meets the Proposition 65 regulatory criteria for listing under the authoritative body mechanism.

Given that ethoprop is no longer formally identified by US EPA as causing cancer, OEHHA prepared this document to provide the CIC with information relevant to the assessment of the evidence of carcinogenicity of ethoprop.

1.1 Background on US EPA Carcinogenicity Reviews of Ethoprop

Between 1997 and 2020, US EPA conducted three evaluations of the carcinogenicity of ethoprop, in 1997, 1998, and 2020. The first and third evaluations (US EPA 1997a, 2020) are available to OEHHA. The 1998[4] evaluation is not available, but US EPA's findings from this evaluation are summarized in the US EPA (2002) Interim Reregistration Eligibility Decision for ethoprop, and in the 2020 evaluation (US EPA 2020).

The US EPA evaluations are summarized below.

US EPA 1997

The carcinogenicity of ethoprop was first reviewed by US EPA in 1997 (provided here as Attachment 1). This review focused on unpublished lifetime feeding studies on ethoprop that were sponsored by the registrant (AMVAC Chemical Corporation). The studies were conducted in male and female Crl:CD®(SD)BR VAF/Plus (Sprague-Dawley or SD derived) rats (Williams 1992), F344 rats (two sets of studies: Spicer (1985) and Barnett et al. (1983)), and $B6C3F_1$ mice (Inoue 1984). US EPA (1997a) considered the F344 rat studies by Barnett et al. (1983) to be "supplementary because a NOEL [no

[4] US Environmental Protection Agency (US EPA 1998). Health Effects Division (HED) Cancer Assessment Review Committee (CARC) Ethoprop – Review of Registrant's Rebuttal to HED's Cancer Classification (dated 10/7/98) TXR 0012890. Office of Pesticide Programs, Washington, DC.

observed effect level] was not established and the number of tissues examined microscopically was not evident to the Agency reviewer." A number of unpublished genotoxicity studies were also considered, including a *Salmonella typhimurium* reverse gene mutation assay, a Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay, a mouse lymphoma L5178Y cell forward gene mutation assay, a CHO cell chromosome aberration assay, an *in vivo* rat bone marrow cytogenetic assay, an *in vivo* rat dominant lethal assay, two *in vitro* unscheduled DNA synthesis assays in primary rat hepatocytes, and an *in vitro* CHO cell sister chromatid exchange assay. US US EPA (1997a) also considered an unpublished metabolism study, and a published structure-activity relationship analysis of ethoprop and other organophosphorus compounds (Woo et al. 1996).

In its evaluation of the carcinogenicity studies, US EPA (1997a) concluded that the dose levels tested "were adequate to assess the carcinogenic potential of Ethoprop." The US EPA noted that in all of the studies "the principal toxicological effects were inhibition of plasma, red blood cell and/or brain cholinesterase activity as well as decreases in body weight gains. The degree of cholinesterase inhibition observed at most doses was considered to constitute "excessive" toxicity in the rats; however, the absence of clinical cholinergic signs of toxicity along with little, if any, frank pathology and increased or comparable survival in treated rats was inconsistent."

US EPA (1997a) classified ethoprop as a "likely" human carcinogen based on the (i) presence of a rare and life-threatening malignant tumor, adrenal pheochromocytoma, in male SD rats in the low dose group in the absence of cholinesterase inhibition, (ii) occurrence of thyroid C-cell carcinomas in two strains of male rats (SD and F344) in three studies at doses that did cause cholinesterase inhibition, and (iii) evidence of clastogenicity *in vitro*. US EPA (1997a) considered the presence of follicular cell tumors evidence that the thyroid is a target organ for ethoprop carcinogenicity.

US EPA 1998

Following the US EPA (1997a) classification, the registrant submitted historical control data of tumor incidences to challenge the cancer classification. After reviewing these data, US EPA reaffirmed in 1998 that ethoprop remained as a "likely" human carcinogen ((US EPA 2002) [see page 14], (US EPA 2020) [see page 6]; provided here as Attachments 2 and 3).

US EPA 2020

In 2020, the US EPA re-assessed the overall carcinogenic evidence of ethoprop (US EPA 2020; provided here as Attachment 3) in response to the registrant AMVAC

Chemical Corporation's submission of unpublished third-party histopathology re-analyses of adrenal and thyroid C-cell tumors in one male SD rat study (Williams 1992) and thyroid C-cell tumors in one male F344 rat study (Spicer 1985) by a pathology working group (PWG) (Hardisty 2017a, b). US EPA (2020) accepted the PWG re-analyses submitted by the registrant but rather than use the unpublished statistical analyses provided by the registrant (Ceuppens and Peers 2017), the US EPA performed its own statistical analyses.

After reviewing the submitted PWG reports and performing new statistical analyses of the adrenal tumor data and the thyroid C-cell tumor data resulting from the PWG re-evaluation of the male SD rat study by Williams (1992), US EPA (2020) concluded that the benign and malignant adrenal pheochromocytomas observed in this study were not treatment-related. The reasoning was that, while the incidence of malignant adrenal pheochromocytomas was above the historical control range, there was no dose-response, and no adrenal medulla hyperplasia was observed. In addition, US EPA (2020) also concluded that the thyroid C-cell tumors observed in the study by Williams (1992) were not treatment-related. US EPA indicated that thyroid C-cell tumors are common in rats with a high and variable spontaneous incidence, and stated "the incidence of thyroid C-cell carcinomas at the high dose (400 ppm) was outside the range of appropriate historical control data, but there was no pairwise statistically significant difference in comparison to concurrent controls."

After reviewing the submitted PWG report and performing new statistical analyses of the thyroid C-cell tumor data resulting from the PWG re-evaluation of the male F344 rat study by Spicer (1985), US EPA (2020) noted that the significant trend ($p < 0.01$) for combined thyroid C-cell adenomas and carcinomas was driven mainly by adenomas, and that there was a significant trend ($p < 0.01$) for adenoma incidence alone. US EPA (2020) concluded that the statistically significant increase in thyroid C-cell tumors in the high dose was treatment-related. In reaching this conclusion US EPA (2020) compared the thyroid C-cell tumor incidence observed in Spicer (1985) to the historical control range reported for NTP studies of male F344 rats by Haseman et al. (1998), noting that the incidence of thyroid C-cell adenoma was within the historical control range, while the incidence of thyroid C-cell carcinoma was outside of the historical control range. US EPA (2020) further stated that the combined incidence of thyroid C-cell adenomas and carcinomas at the high dose (100 ppm) was statistically significant by pairwise comparison ($p < 0.05$), and that the dose was not excessive, as reduced cholinesterase activity occurred without mortality or serious toxicity.

In re-assessing the overall carcinogenic evidence of ethoprop in 2020, US EPA did not consider the findings from the F344 rat studies by Barnett et al. (1983), stating that these studies, which included preconception, *in utero*, lactational, and direct exposure

through week 112 of life, were not acceptable and “not designed to evaluate carcinogenicity.”

In the 2020 assessment, US EPA reclassified ethoprop as “Suggestive Evidence of Carcinogenic Potential,” based on “the presence of one tumor type, thyroid C-cell tumors, which occurred in only one sex (males) and one species (F344 rat) and no mutagenicity concerns.”

1.2 Chemical Identity of Ethoprop

Ethoprop is an organophosphate ester and is in an organophosphate subclass called phosphorodithioates, where two sulfur atoms are bound to the phosphorus atom (Caceres et al. 2010). The chemical structure of ethoprop is shown in Figure 1. Ethoprop is a pale yellow liquid at room temperature and has a strong mercaptan odor. Selected chemical properties of ethoprop are listed in Table 1. With its moderate octanol-water coefficient, ethoprop is moderately soluble in water and is soluble in most organic solvents (e.g., ethanol or acetone).

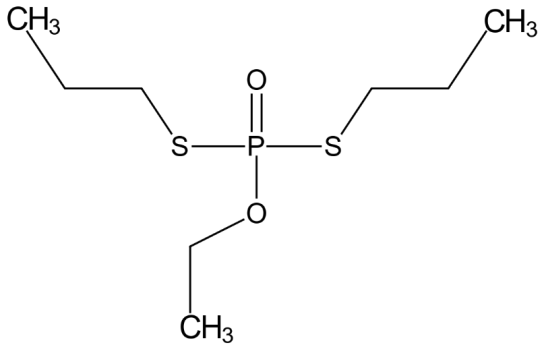


Figure 1. Chemical structure of ethoprop

Table 1. Selected chemical properties of ethoprop[1]

Chemical name	Ethoprop
Synonyms	Ethoprophos; *O*-Ethyl S,S-dipropyl phosphorodithioate (IUPAC name); Phosphorodithioic acid; *O*-Ethyl S,S-dipropyl ester; Mocap® (trade name)
Chemical Abstracts Service Registry Number	13194-48-4
Molecular formula	$C_8H_{19}O_2PS_2$
Molecular weight (g/mol)	242.3
Boiling point (ºC)	244
Melting point (ºC)	-1.14
Vapor pressure (mmHg)	4.03e-4
Water solubility (mol/L)	3.56e-3
Octanol-water coefficient (Log K_{ow})	3.59
Octanol-air coefficient (Log K_{oa})[2]	8.64

1. Values are from US EPA's CompTox Chemical Dashboard (https://comptox.epa.gov/dashboard/chemical/details/DTXSID4032611; accessed January 27, 2026).
2. A predicted value; all other values reported in Table 1 are measured data.

1.3 Production, Sources, and Use

Ethoprop is a man-made organophosphate pesticide used as an insecticide, nematicide, and fungicide and sold under the trade name Mocap®. Organophosphate pesticides inhibit cholinesterase and block the breakdown of acetylcholine, resulting in neurotoxicity.

Ethoprop has been registered as a pesticide under the US EPA since 1967 and is also registered with CDPR. Due to its acute toxicity, ethoprop is a restricted use pesticide and can only be purchased and used by certified applicators (or persons under the direct supervision of certified applicators) for specific certified uses with required personal protective equipment (PPE), such as gloves and respirators (CDPR 2026a). There is no residential use of ethoprop. Pests targeted by ethoprop include moths, beetles, insects and nematodes. Ethoprop is applied directly to the soil before or at the time of planting, or during pre-emergence or post-harvest periods. Application directly to water is not permitted.

Usage data in the US from 1987 to 1996 reported an average annual domestic use of roughly 700,000 pounds (lbs) of ethoprop, while data provided by the registrant for the

years 1998 to 2000 indicated that domestic use was about 1 million lbs per year (US EPA 2006). The estimated usage of ethoprop in the US in 2012 was less than 1 million lbs (US EPA 2017).

Currently in California there are three registered ethoprop products from a California-based registrant, AMVAC Chemical Corporation (CDPR 2026a): Mocap® 15% Granular Nematicide-Insecticide (containing 15% ethoprop), Mocap® 15% Granular Lock'n Load Closed Loading System, and Mocap® EC (emulsifiable concentrate; containing 69.6% ethoprop) Nematicide-Insecticide. Use of ethoprop in California over the last 10 years has been rising (Figure 2) (CDPR 2026d). In 2014, 3,076 lbs of ethoprop were used in California and the usage nearly doubled by 2018 to 5,848 lbs. In 2023 (the most recent data from CDPR (2026d)), about 13,000 lbs of ethoprop were applied to sweet potato (58%), potato (30%), outdoor nursery flowers (5%), cabbage (3%), dried beans (2%) and rights of way (2%) across ten California counties (Del Norte, Fresno, Imperial, Merced, Monterey, San Benito, San Joaquin, San Luis Obispo, Santa Barbara, and Stanislaus).

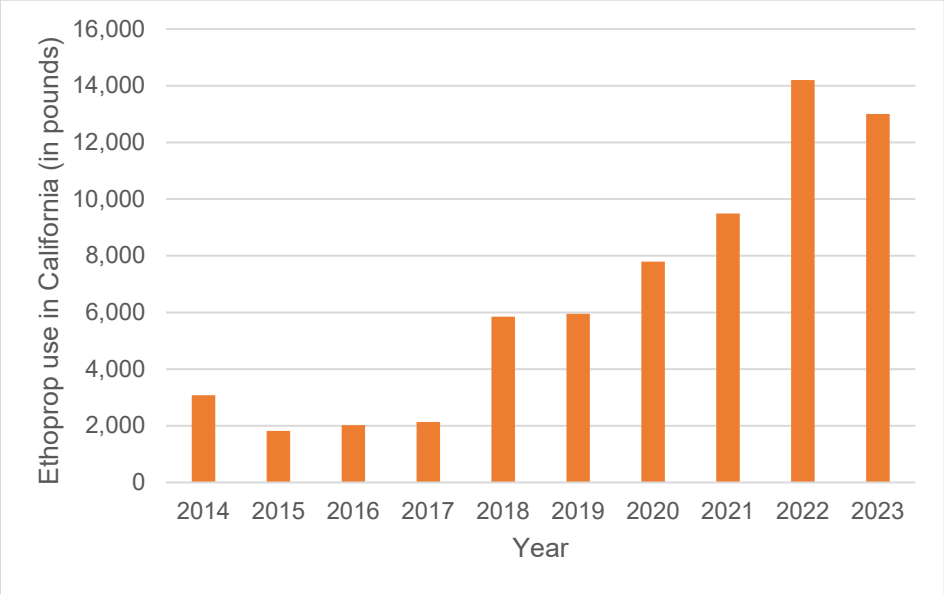


Figure 2. Ethoprop use in California from 2014-2023 (in pounds; CDPR PUR; data accessed on 9/29/2025)

1.4 Occurrence and Exposure

Ethoprop is volatile and water soluble with low persistence and moderate mobility in the environment. As a result, ethoprop has been detected in the air (Cordoba Gamboa et al. 2020; Coscollà et al. 2010; Lunchick et al. 2005; Peck and Hornbuckle 2005; Solano Diaz et al. 2026), particulate matter with a diameter less than 10 micrometers (μm)

(PM_{10}) (Hart et al. 2012; Lopez et al. 2017), and water (CDPR 2026b, c; Dahshan et al. 2016; Du et al. 2017; Echeverría-Sáenz et al. 2012; Gruber and Munn 1998; Lisker et al. 2011; SWAMP 2025; USDA 2026a).

Based on data reported in the US EPA's Toxics Release Inventory (TRI), 8,342 lbs of ethoprop were emitted into the air in the US in 2024 from a single stationary source in California, AMVAC Chemical Corporation.

Personal monitoring data of pesticide applicators (sampling duration up to 545 minutes during workdays) in Washington state showed that air concentrations of ethoprop in the applicators' breathing zones ranged between 0.0001 to 0.01 microgram per liter (µg/L) (equal to 0.1–10 microgram per cubic meter (µg/m^3)) during active ethoprop applications in potato fields (Lunchick et al. 2005). No occupational exposure standards for ethoprop have been identified in the US, and no acute pesticide illnesses or injuries related to use of ethoprop were reported in the California Pesticide Illness Query (CalPIQ) system from 1992 to 2023.

Ethoprop has been detected in the air from several studies with different sampling methods (and detection limits (DL)): 24-hour air samples taken in Iowa, US (Peck and Hornbuckle 2005), 1-week air samples in France (Coscollà et al. 2010), 1- to 7-week passive air samples taken in Costa Rica (Cordoba Gamboa et al. 2020; Solano Diaz et al. 2026), and 24-hour PM_{10} samples taken in Spain (Hart et al. 2012; Lopez et al. 2017). Air concentrations of ethoprop from these studies were generally low, in the range of non-detected to a maximum of 60.9 nanogram per cubic meter (ng/m^3) (equal to 0.0609 µg/m^3).

The half-life of ethoprop is 133 days in water (NCRWQCB 2021). Most data on surface water samples collected in the US or other countries show non-detectable to low levels (in parts per billion (ppb) range) of ethoprop. In CDPR's Surface Water Database (SURF), ethoprop was not detected in 2024 in the more than 90 surface water samples collected in California agricultural areas (CDPR 2026b, c). In the same SURF database from 1992 to 2010, only 1.1% (= 46/4176) of surface water samples had detectable ethoprop, with the maximum concentration at 1.11 µg/L (= ppb) (Lisker et al. 2011). Another California study (SWAMP 2025) reported that 6 out of 63 (= 9.5%) surface water samples taken between 2021–2024 near lily bulb fields treated with ethoprop in the North Coast region had ethoprop above the detection limit (DL not specified but less than 0.0044 ppb), with a maximum concentration of 2 ppb measured in those samples. Additional US surface water samples collected from two lakes in Washington (Gruber and Munn 1998) and highway runoff in Missouri and Washington had concentrations of ethoprop ranging from non-detectable (DL: 0.003 ppb) to a maximum of 0.12 ppb.

In the national pesticide database collected by the US Department of Agriculture (USDA 2026a), ethoprop was detected in only one of more than 8,000 water samples (with

detection limits ranging from 3,000–17,000 ppb) from bottled water, groundwater, and untreated or finished water samples collected from 1994 to 2024; that one sample of finished water was collected in Minnesota and had an ethoprop concentration of 27,000 ppb.

Ethoprop does not strongly adsorb to soil and is considered to have moderate to high mobility potential in soil. The major mechanism of dissipation for ethoprop in soil is degradation though microbial metabolism (CDPR 1995). For example, *Flavobacterium sp*. (a gram-negative bacteria) can hydrolyze ethoprop (Ortiz-Hernández et al. 2003). The half-life of ethoprop in soil varies by soil characteristics (e.g., pH, organic content) and has been variously estimated to be 6.8–16.8 days (Chin-Pampillo et al. 2015) and 9–42 days (Jones and Norris 1998).

US EPA set a tolerance level for ethoprop in several raw agricultural commodities (e.g., sweet potato, potato, banana, bean, corn, hop, and mint) at 0.02 ppm (CFR 2026). This tolerance level has rarely been exceeded based on multiple-year pesticide monitoring databases collected by the USDA and CDPR. From 1994 to 2024, only two out of over 168,400 samples from the USDA Pesticide Data Program had ethoprop residue levels exceeding 0.02 ppm: one sweet bell pepper sample (no tolerance level set) collected in 2000 in California with 0.024 ppm ethoprop and one banana sample collected in 2002 in Texas with 0.025 ppm Ethoprop (USDA 2026b). Ethoprop was not detected in over 41,000 agricultural product samples collected in California from 2020 to 2023 (CDPR Annual Residue Data). Ethoprop may be taken up by the root system of plants and extensively metabolized (CDPR 1995).

In addition to the US data on ethoprop residues in agricultural commodities, several international studies have evaluated ethoprop levels in food. In these countries, ethoprop has been detected in vegetables (Aris et al. 2020; Chun and Kang 2003; Wang et al. 2013), rice (Aris et al. 2020), honey (Cunha et al. 2024), common carp (Fu et al. 2018), and baby formula (Dobrinas et al. 2016) with maximum levels less than 0.02 ppm in most cases, except sampled rice (2.52 ppm) and cabbage (2.45 ppm) from Malaysia (Aris et al. 2020) and some vegetables (e.g., lettuce, pepper) from Korea (Chun and Kang 2003). Ethoprop was not detected in coho salmon tissues from Washington, US (Du et al. 2017).

Humans may be exposed to ethoprop via the dermal, inhalation, and ingestion routes. Dermal exposure occurs when workers' skin is in contact with ethoprop through loading, mixing, or applying ethoprop. Dermal intake can be reduced with proper PPE, such as protective clothing, and hand-washing practices. Inhalation of volatile ethoprop by workers can be mitigated by use of respirators. While ingestion of ethoprop via contaminated food or water is possible, as discussed above, concentrations reported in US produce, fish, and water are generally low. Occupational exposure (e.g., pesticide

applicators) is likely to be higher than exposure in the general population. The primary route of occupational exposure to ethoprop is likely to be dermal, with inhalation contributing a much lesser extent (Lunchick et al. 2005; Meinders and Ross 1996).

1.5 Reviews by Other Health Agencies

As presented in Section 1.1, ethoprop has been reviewed by US EPA as to its potential carcinogenicity (in 1997, 1998, and 2020) and US EPA currently classifies ethoprop as "Suggestive Evidence of Carcinogenic Potential" (US EPA 2020). Ethoprop has not been classified with regard to carcinogenicity by the International Agency for Research on Cancer (IARC), 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 2018, the European Food Safety Authority (EFSA 2018) classified ethoprop as a Category 2 carcinogen ("suspected of causing cancer") according to their classifying, labeling, and packaging (CLP) criteria. EFSA's evaluation of ethoprop related to carcinogenesis (EFSA 2018) is briefly summarized below:

- Different tumor findings were observed in two strains of rats in independent cancer bioassays:
    - Malignant pheochromocytoma;
    - Thyroid C-cell carcinoma;
    - Uterus endometrial adenoma and carcinoma.
- The potential for genotoxicity or clastogenicity could not be ruled out because of several positive and inconclusive results, and some identified data gaps.
- The carcinogenic modes of action (MOA) have not yet been investigated; however, a genotoxic MOA cannot be excluded.

2. OVERVIEW OF SYSTEMATIC LITERATURE REVIEW APPROACH

2.1 Literature Search Process

Literature searches on the carcinogenicity of ethoprop were initiated in October 2025 and last updated in August 2026. 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. In addition, because ethoprop is a pesticide, toxicity data submitted by pesticide registrants to CDPR and US EPA were requested and reviewed.

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 2025).

The searches were conducted by OEHHA scientists using the following approaches:

- Primary searches in major biomedical databases.
- Searches in other data sources, including authoritative reviews and reports, and databases or web resources.
- Requests to CDPR and US EPA for toxicity data submitted by pesticide registrants.
- Additional focused searches.

Literature searches were supplemented with a public data call-in period from December 19, 2025, to February 2, 2026; no submissions were received.

Primary searches for ethoprop were executed using the chemical name and 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 for cancer studies in humans, 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

As part of a systematic review approach, populations, exposures, comparators and outcomes (PECO) criteria and descriptions of potentially relevant supplemental materials were used to screen the primary literature search results (see Appendix A).

Health Assessment Workspace Collaborative (HAWC, https://hawcproject.org) (Shapiro et al. 2018) was used as a tool to facilitate the screening and tagging of the results of the primary literature search. 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.

In Level 1 screening in HAWC, each citation was first screened by two OEHHA scientists, using PECO criteria and descriptions of supplemental materials based solely on titles and abstracts to eliminate studies or articles that do not meet the PECO criteria or contain information on any of the key topics identified as potentially relevant supplemental material. 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 the same PECO criteria and descriptions of supplementary materials used in the Level 1 screening. Eligibility of any study that met PECO or supplemental material criteria was independently confirmed by another OEHHA scientist.

Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC.

Total references

More than 150 references, including peer-reviewed journal articles, government reports, and pesticide registrant studies, were identified for inclusion through these search strategies. Among these, over 80 references were cited in this document.

3. CARCINOGENICITY STUDIES IN HUMANS

No cancer epidemiology studies on the effects of human exposure to ethoprop were identified in the literature search conducted by OEHHA (Appendix A).

4. CARCINOGENICITY STUDIES IN ANIMALS

OEHHA identified multiple carcinogenicity studies of ethoprop in animals, with six studies in rats and four studies in mice (Table 2). All of these studies were conducted on behalf of pesticide registrants, and most were submitted to US EPA; none have been published in the peer-reviewed scientific literature. OEHHA obtained these studies from either the US EPA (Ceuppens and Peers 2017; Hardisty 2017a, b) through a Freedom of Information Act request after signing a confidentiality agreement or CDPR (Barnett et al. 1983, Davison and Voss 1983; Inoue 1984; Spicer 1985; Williams 1992) through a confidentiality agreement. The public may obtain access to these studies in the same manner as OEHHA, by contacting US EPA and CDPR, respectively. Ethoprop was administered via the diet in all studies, with exposure in two rat studies including pre-conceptional, *in utero*, and lactational exposure, and continuing until week 112 of life.

Of the rat studies, two were conducted in SD-derived Crl:CD®(SD)BR VAF/Plus rats for 104 weeks (US EPA 1997a, 2020; Williams 1992), two were conducted in Fischer 344

(F344) rats for 105 weeks (Spicer 1985; US EPA 1997a, 2020), and two additional studies in F344 rats involved exposures starting at preconception and continuing until week 112 of life (Barnett et al. 1983; US EPA 1997a, 2020).

Of the studies in mice, all were in $B6C3F_1$ mice, with two conducted for 104 weeks (Inoue 1984) and two conducted for 78 weeks (Davidson and Voss 1983). The mouse studies conducted by Davidson and Voss (1983) had a number of serious limitations, including inadequate characterization of the technical grade substance tested, incomplete reporting, reporting errors, dosing errors (i.e., administration of 10X the intended dose, resulting in the death of 18 mice in the male study and nine mice in the female study), other survival issues (e.g., unusual losses in the male study by week 21 in both control and treated animals), and less-than-lifetime study duration. These studies of Davidson and Voss (1983) are of limited informativeness due to these limitations, were not mentioned or discussed in the US EPA 1997a or 2020 evaluations of ethoprop (US EPA 1997a, 2020) and are not discussed further (See Appendix B for more details on these studies).

All of these studies, with the exception of the 78-week dietary studies in male and female $B6C3F_1$ mice by Davidson and Voss (1983), are summarized below.

Table 2. Overview of ethoprop carcinogenicity studies in rats and mice

No.	Species, strain	Sex, group size[1]	Route, age at first exposure (weeks)	Administered concentration (ppm)	Exposure duration (weeks)	Reference
1	Rat, Crl:CD®(SD)BR VAF/Plus	M, 70	Diet, 6	0, 1, 60, 400	104	Williams 1992; US EPA 1997a & 2020
2	Rat, Crl:CD®(SD)BR VAF/Plus	F, 70				
3	Rat, F344	M, 50	Diet, 6	0, 1, 10, 100	105	Spicer 1985: US EPA 1997a & 2020
4	Rat, F344	F, 50				
5	Rat, F344	M (F_1), 50	F_0: via diet F_1: pre-conception, *in utero*, and through lactation (via F_0), via diet from weaning until 112 weeks of age	0, 49, 98,196[2]	preconception through 112 weeks of age	Barnett et al. 1983
6	Rat, F344	F (F_1), 50				
7	Mouse, B6C3F_1	M, 50	Diet, 5	0, 0.2, 2, 30	104	Inoue 1984; US EPA 1997a
8	Mouse, B6C3F_1	F, 50				
9[3]	Mouse, B6C3F_1	M, 50	Diet, 8–10	0, 15, 30, 60[4]	78	Davidson & Voss 1983
10[3]	Mouse, B6C3F_1	F, 50				

[1] Does not include animals in interim sacrifice groups.

[2]Parental (F_0) animals received 0, 4.5, 9, or 18 ppm ethoprop preconception and throughout gestation and lactation, until weaning of the pups. At weaning, offspring (F_1) of dams receiving 0, 4.5, 9, or 18 ppm ethoprop, respectively, were placed on diets containing 0, 4.5, 9, or 18 ppm ethoprop respectively, from 4 to 12 weeks of age. From 13 weeks of age until termination offspring in these respective groups received 0, 49, 98, or 196 ppm ethoprop in the diet.

[3] These studies had a number of serious limitations, including incomplete reporting, reporting errors, dosing errors, survival issues, and less-than-lifetime study duration and are not discussed further (See Appendix B for more details on these studies).

[4] A dosing error occurred in both the male and female studies during week 54, when animals in the 60-ppm groups were inadvertently administered a dose ten-times higher (600 ppm) than the intended level for one week.

SD, Sprague-Dawley; F344, Fischer 344; ppm, parts per million; M, male; F, female; F_0, breeder/parental animals; F_1, offspring.

4.1 Carcinogenicity Studies of Ethoprop in Rats

4.1.1 104-week feeding studies in male and female Crl:CD®(SD)BR VAF/Plus rats (Williams 1992; US EPA 1997a, 2020; Hardisty 2017a)

104-week dietary studies in male and female Crl:CD®(SD)BR VAF/Plus rats sponsored by Rhone-Poulenc Ag Company were conducted at Hazleton Laboratories America in Wisconsin (Williams 1992, an unpublished study), and study reports were provided to the US EPA (1997a, 2020).

Male and female Crl:CD®(SD)BR VAF/Plus rats (also referred to as SD [Sprague Dawley] rats in this document) obtained from Charles River Laboratories, Inc. were administered ethoprop (95.6% purity) via diet at concentrations of 0, 1, 60, or 400 ppm beginning at 6 weeks of age for 104 weeks. Animals in the 400-ppm groups received 600 ppm ethoprop in the diet for the first two weeks, before the dietary concentration was reduced to 400 ppm for the remainder of the studies due to excessive toxicity (e.g., weight gain depression, tremors, ataxia, death (two deaths occurred in the female rat study)). In these studies, each experimental group was comprised of 70 animals, with 10 additional animals per group included for interim sacrifice at 53 weeks. Respective average daily doses were 0, 0.04, 2.44, 18.38 milligrams per kilogram per day (mg/kg/day) for males, and 0, 0.06, 3.56, 23.98 mg/kg/day for females (US EPA 2020).

These male and female rat studies each included an ancillary “recovery arm”, consisting of separate groups of 10 control animals and 10 animals fed diet containing 400 ppm ethoprop for 52 weeks, followed by a four-week recovery period on basal diet and sacrifice at 57 weeks.

Test diets were prepared by thoroughly mixing the test substance with the basal diet. Histopathological examinations were conducted on all animals in the control and 400-ppm groups in the main studies and in the ancillary “recovery arms”, all animals found dead or moribund in the 1- and 60-ppm groups, and “on macroscopic lesions, lungs, liver, kidneys, and thyroid glands” (Williams 1992, p. 18) from all animals in the 1- and 60-ppm groups. Not all adrenal glands or uteri from the 1- and 60-ppm groups were examined. It was not reported whether the pathologist was aware of or blinded to the treatment status of the animals/tissues during histopathological examination.

Males

In males, there was no significant difference in survival between the controls and the treated groups until week 84, when a statistically significant increase in survival was observed in the 400-ppm group (at weeks 84, 85, and 92–99). Decreases in body weight (11–16%) and food consumption were observed in the 400-ppm group compared

to control throughout most of the study (Williams 1992), with no treatment-related differences in body weight or food consumption observed at the 1- and 60-ppm doses.

Tumors reported in Williams (1992)

Williams (1992) reported that tumors were observed in adrenal and thyroid glands of male SD rats. Table 3 presents the incidence data for adrenal pheochromocytomas, thyroid C-cell tumors, and thyroid follicular cell tumors, as extracted by OEHHA from the individual animal data reported by the study pathologist in Williams (1992). No adrenal or thyroid gland tumors were observed in the 53-week interim sacrifice groups.

In the separate “recovery arm” of the study, where groups of 10 animals each were fed control or 400-ppm diets for 52 weeks followed by a four-week recovery period on basal diet and sacrificed at 57 weeks, one thyroid C-cell adenoma was observed in the control group and two thyroid C-cell adenomas were seen in the 400-ppm dose group. No thyroid follicular cell tumors or adrenal pheochromocytomas were observed in the “recovery arm” of the study.

In Table 3 OEHHA presents the tumor incidence data as effective number (i.e., the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site), as well as findings from statistical tests conducted by OEHHA (i.e., Fisher’s exact pairwise test and Cochran-Armitage exact trend test, referred to as the exact trend test). Tumor incidence data reported by US EPA (1997a) and findings from statistical tests conducted by US EPA (1997a) are presented in footnotes to Table 3.

As shown in Table 3, malignant pheochromocytomas of the adrenal gland were observed in treated males, but not in controls; however, these increases were not statistically significant when analyzed by OEHHA by applying either Fisher’s exact pairwise test or the exact trend test to tumor incidence data expressed as effective number. As noted above, not all adrenal glands were examined in the 1- and 60-ppm groups, and OEHHA acknowledges that due to selection bias in adrenal gland examination, the statistical tests conducted using the 1- and 60-ppm groups are likely biased. As explained in some detail in footnote 1 of Table 3, US EPA (1997a) reported a statistically significant increase in adrenal malignant pheochromocytoma in the 400-ppm group ($p < 0.005$), using Peto’s prevalence pairwise test to analyze tumor incidence data expressed as effective number (i.e., the number of tumor bearing animals over the number of animals examined, excluding those that died or were sacrificed before observation of the first tumor) from the control and 400-ppm groups. Discrepancies in adrenal tumor incidence reported by OEHHA and US EPA (1997a) are also noted in that footnote.

As shown in Table 3, increases in thyroid C-cell adenoma, carcinoma, and adenoma and carcinoma combined were observed, with statistically significant dose-related trends in the incidences of C-cell carcinoma and C-cell adenoma and carcinoma combined (as analyzed by OEHHA by applying the exact trend test to tumor incidence data expressed as effective number). As explained in footnote 2 of Table 3, US EPA (1997a) reported a statistically significant increase in thyroid C-cell carcinoma in the 400-ppm group ($p = 0.042$) using a pairwise Peto's prevalence test, with a statistically significant trend using Peto's prevalence trend test to analyze tumor incidence data expressed as effective number (i.e., the number of tumor bearing animals over the number of animals examined, excluding those that died or were sacrificed before observation of the first tumor). The discrepancy in thyroid C-cell carcinoma incidence reported by OEHHA and US EPA (1997a) is also noted in that footnote.

Table 3 also shows that increases in thyroid follicular cell adenoma and adenoma and carcinoma combined were observed, with the increase in thyroid follicular cell adenoma in the 400-ppm group compared to control reaching statistical significance ($p \leq 0.05$, as analyzed by OEHHA by applying Fisher's exact pairwise test to tumor incidence data expressed as effective number). As indicated in footnote 3 of Table 3, US EPA (1997a) reported that the increases in thyroid follicular cell adenoma were statistically significant in all treated groups compared to control ($p < 0.05$), applying Peto's prevalence pairwise test to incidence data expressed as effective number (i.e., the number of tumor bearing animals over the number of animals examined, excluding those that died or were sacrificed before observation of the first tumor). Discrepancies in thyroid follicular cell tumor incidence reported by OEHHA and US EPA (1997a) are also noted in that footnote.

Table 3. Incidence of adrenal pheochromocytomas, thyroid C-cell tumors, and thyroid follicular cell tumors in male SD rats administered ethoprop in the diet for 104 weeks, based on tumor identification by study pathologist (Williams 1992, US EPA 1997a)

Tumor site	Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test *p* value by OEHHA
		0	1	60	400	
		Daily dose (mg/kg/day)				
		0	0.04	2.44	18.38	
Adrenal[1]	Benign pheochromocytoma (614)	14/49	7/25	7/28	5/61	NS
	Malignant pheochromocytoma (654)	0/41	2/16	2/18	5/58	NS
	Benign and malignant pheochromocytoma (combined) (614)	14/49	8/25	9/28	10/61	NS
Thyroid	C-cell adenoma (416)	8/66	6/67	9/67	12/68	NS
	C-cell carcinoma[2] (492)	0/61	0/63	1/63	3/66	< 0.05
	C-cell adenoma and carcinoma (combined) (416)	8/66	6/67	10/67	15/68	< 0.05
	Follicular cell[3] adenoma (574)	0/52	4/56	4/55	5/63*	NS
	Follicular cell[3] carcinoma (694)	1/34	0/31	1/36	1/51	NS
	Follicular cell[3] adenoma and carcinoma (combined) (574)	1/52	4/56	5/55	6/63	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site (based on review of data reported in Williams (1992)). Fisher's exact pairwise and Cochran-Armitage exact trend tests conducted by OEHHA. * $p \leq 0.05$; NS: not significant. Daily doses in mg/kg/day from US EPA (2020).

[1] US EPA (1997a) stated that the adrenal tumor incidence data for the 1 and 60-ppm groups were excluded from statistical analyses since not all animals in these groups were examined microscopically for adrenal gland pheochromocytomas. US EPA (1997a) reported that there was a statistically significant increase ($p = 0.005$) in malignant pheochromocytoma in the 400-ppm group with incidence of 0/41 and

5/60 at 0 and 400 ppm, respectively, using Peto's prevalence test (Table 3 in US EPA 1997a). However, OEHHA obtained a *p*-value of < 0.05 and > 0.01 when running Peto's test using the US EPA (1997a) incidence and cause-of-death data. The reason for the discrepancy between OEHHA and US EPA (1997a) in the incidence of adrenal malignant pheochromocytoma in the 400-ppm group is unclear, as are the reasons for additional discrepancies (i.e., in the 1-ppm group US EPA (1997a) reported incidence of benign pheochromocytoma as 7/26 and incidence of benign and malignant pheochromocytoma (combined) as 8/26).

[2] US EPA (1997a) reported that there was a statistically significant increase ($p = 0.042$) in thyroid C-cell carcinomas in the 400-ppm group with incidence of 0/61, 0/63, 1/64, 3/66 at 0, 1, 60, and 400 ppm, respectively, with a significant dose-related trend ($p = 0.014$) using Peto's prevalence test (Table 4 in US EPA 1997a). The reason for the discrepancy between OEHHA and US EPA (1997a) in the incidence of thyroid C-cell carcinoma in the 60-ppm group is unclear.

[3] US EPA (1997a) reported statistically significant ($p \leq 0.05$) increases in thyroid follicular cell adenomas by pairwise comparisons for each dose group with control, using Peto's pairwise tests and incidence of 0/53, 4/56, 4/56, 5/63 at 0, 1, 60, and 400 ppm, respectively (Table 5 in US EPA 1997a). The reason for the discrepancies between OEHHA and US EPA (1997a) in the incidence of thyroid follicular cell adenoma in the control and 60-ppm groups is unclear, as are the reasons for additional discrepancies (i.e., in the control group US EPA (1997a) reported incidence of follicular cell adenoma and carcinoma (combined) as 1/53; in the 60-ppm group US EPA (1997a) reported incidence of follicular cell adenoma and carcinoma (combined) as 5/56).

PWG re-evaluation of Williams (1992) male rat adrenal pheochromocytomas and thyroid C-cell tumors (Hardisty, 2017a)

A pathology working group (PWG) organized by the registrant, AMVAC Chemical Corporation, re-evaluated the adrenal pheochromocytoma and thyroid C-cell tumor histopathology slides from the Williams (1992) male SD rat study (Hardisty 2017a, an unpublished study) (including slides from the week 53 interim sacrifice animals and slides from the ancillary "recovery arm" of the study). The US EPA accepted the findings of that re-evaluation, with some modifications with regard to the total number of malignant pheochromocytomas observed in the 1-ppm group (US EPA 2020). Specifically, the PWG (Hardisty 2017a) reported three animals in the 1-ppm group with malignant pheochromocytoma, based on re-evaluation of the histopathology slides, while US EPA (2020) reported four animals in this dose group and noted that "For one rat of this group, animal no. C39512, a unilateral malignant pheochromocytoma was not available for review". After reviewing the available data (Hardisty 2017a; US EPA 2020; Williams 1992) OEHHA agrees with US EPA (2020) that there were four animals with malignant pheochromocytoma in the 1-ppm dose group. This is supported by adrenal tumors being reported as the cause of death for this animal (Williams 1992) and by information that only one adrenal gland from animal C39512 was re-evaluated by the PWG (Hardisty 2017a).

In re-evaluating the adrenal pheochromocytoma and thyroid C-cell tumor histopathology slides from the main study, the PWG did not observe any tumors in the 53-week interim sacrifice groups, consistent with the findings in the original study report.

In the separate “recovery arm” of the male rat study, the PWG evaluation was consistent with the original evaluation in Williams (1992), i.e., one thyroid C-cell adenoma in the control group and two thyroid C-cell adenomas in the 400-ppm group.

In Table 4 OEHHA presents the incidence data for adrenal pheochromocytomas and thyroid C-cell tumors as effective number (i.e., the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site), based on the PWG re-evaluation, using information reported in Hardisty (2017a), together with the information discussed above from US EPA (2020) regarding the number of adrenal malignant pheochromocytomas observed in the 1-ppm dose group. Analyzing these data using Fisher’s exact pairwise test and Cochran-Armitage exact trend test, OEHHA observed a statistically significant increase in adrenal malignant pheochromocytoma in the 1-ppm group, as determined by pairwise comparison with control using Fisher’s exact pairwise test. No dose-related trend was observed by the Cochran-Armitage exact trend test (Table 4). OEHHA also observed statistically significant trends in the incidence of thyroid C-cell carcinoma and C-cell adenoma and carcinoma (combined) using the Cochran-Armitage exact trend test (Table 4). Tumor incidence data reported by US EPA (2020) and findings from statistical tests conducted by US EPA (2020) are presented in footnotes to Table 4.

Table 4. Incidence of adrenal pheochromocytomas and thyroid C-cell tumors in male SD rats administered ethoprop in the diet for 104 weeks (Williams 1992), based on tumor identification by the PWG re-evaluation (Hardisty 2017a; US EPA 2020)

Tumor site	Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test *p* value by OEHHA
		0	1	60	400	
		Daily dose (mg/kg/day)				
		0	0.04	2.44	18.38	
Adrenal[1]	Benign pheochromocytoma (614)	15/49	4/25	6/28	5/61	NS
	Malignant pheochromocytoma (651)	1/42	4/16*[2]	2/19	5/60	NS
	Benign and malignant pheochromocytoma (combined) (614)	16/49	8/25	8/28	10/61	NS
Thyroid[3]	C-cell adenoma[4] (416)	10/66	6/67	9/67	13/68	NS
	C-cell carcinoma (492)	0/61	0/63	1/63	3/66	< 0.05
	C-cell adenoma and carcinoma (combined) (416)	10/66	6/67	10/67	16/68	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive and examined at the time of first tumor occurrence. Fisher's exact pairwise and Cochran-Armitage exact trend tests conducted by OEHHA. NS: not significant. * $p < 0.05$ for pairwise comparison with controls.

[1] Not all adrenal glands in animals from the 1- and 60-ppm groups were examined (Williams 1992).

[2] $p < 0.05$ from Fisher's exact pairwise test conducted by OEHHA. This increase in adrenal malignant pheochromocytoma was also reported by the US EPA (2020, Table 15) using Peto's prevalence test [1/40, 4/19 (p <0.05), 2/20, 5/60 at 0, 1, 60, and 400 ppm, respectively]. The reason for the discrepancies between OEHHA and US EPA (2020, Table 15) in the incidence of adrenal malignant pheochromocytoma in the control, 1- and 60-ppm groups is unclear. US EPA (2020, Table 15) reported the incidences of adrenal benign pheochromocytoma as 14/47, 4/26, 6/28, and 5/61 and adrenal benign and malignant pheochromocytoma (combined) as 15/47, 8/26, 8/28, and 10/61 for the control, 1-, 60-, and 400-ppm groups, respectively. The reason for the discrepancies between OEHHA and US EPA (2020) in the reporting of benign pheochromocytoma in the control and 1-ppm groups, and the reporting of benign and malignant pheochromocytoma (combined) in the control, and 1-ppm groups is unclear.

[3] US EPA (2020, Table 14) reported a statistically significant dose-related trend in thyroid C-cell carcinomas using Peto's prevalence test, but not in thyroid C-cell adenomas and carcinomas (combined). US EPA (2020, Table 14) reported the incidences of thyroid C-cell adenomas as 11/76, 6/67, 10/67, and

15/78, thyroid C-cell carcinoma as 0/60, 0/63, 1/64, and 3/66, and thyroid C-cell adenoma and carcinoma (combined) as 11/76, 6/67, 11/67, and 18/78 for the control, 1-, 60-, and 400-ppm groups, respectively. The reason for the discrepancies between OEHHA and US EPA (2020, Table 14) in the reporting of thyroid C-cell adenoma in the control, 60-, and 400-ppm dose groups, the reporting of thyroid C-cell carcinoma in the control and 60-ppm dose groups, and the reporting of thyroid C-cell adenoma and carcinoma (combined) in the control, 60- and 400-ppm dose groups is unclear, but may partially be due to US EPA including the "recovery arm" animals in the numerators and denominators.

[4] OEHHA found a data discrepancy in the reporting of thyroid C-cell adenomas between US EPA (2020) and Hardisty (2017a): Hardisty (2017a) reported 9 tumor-bearing animals in the 60-ppm group, while US EPA (2020) reported 10 tumor-bearing animals in this dose group. No explanation for the discrepancy was provided.

Non-neoplastic findings

No dose-related increases in adrenal medullary or thyroid C-cell hyperplasia were observed in male rats.

Dose-dependent reductions in cholinesterase (plasma, red blood cell, and brain) activities were observed at 104 weeks. At 104 weeks, plasma, red blood cell, and brain cholinesterase activities were reduced by 63, 34, and 33% in the 60-ppm group, and by 77, 41 and 64% in the 400-ppm group, reaching pairwise significance. Cholinesterase activities were also measured in the control and the 400-ppm group at week 57: plasma, red blood cell and brain activities were reduced by 21, 25 and 4% in the 400-ppm group compared to the controls.

Anemia was observed in the 400-ppm group. No cholinergic signs of toxicity were reported in any of the treated groups.

Females

In females, there was no significant difference in survival between the controls and the treated groups until week 89, when a statistically significant increase in survival was observed in the 400-ppm group (at weeks 89, 92, and 97 to 103). Decreases in body weight (10 to 20%) were observed in the 400-ppm group compared to control throughout most of the study. Food consumption was significantly decreased in this dose group at week 2. Following the reduction in the administered dose from 600 ppm to 400 ppm, animals in this group consumed more food than controls during week 4. Decreased food consumption in the 400-ppm group was statistically significantly decreased compared to controls from week 6 through 22 and sporadically from weeks 28 to 84, *i.e*. weeks 28, 36, 38, 44, 72, 76, and 84.

Tumors reported in Williams (1992)

Williams (1992) reported that endometrial stromal polyps were observed in the uterus of female SD rats during the 104-week study. Endometrial stromal polyps are classified as common, benign tumors of the uterus in female rats (Dixon et al. 2018). Table 5

presents the incidence data for these uterine tumors, as extracted by OEHHA from the individual animal data reported by the study pathologist. Endometrial stromal polyps were observed in the 53-week interim sacrifice groups, and thus the data from the 53-week interim sacrifice groups are included in the incidence data presented in Table 5.

In a separate “recovery arm” of the study, where groups of 10 animals each were fed control or 400-ppm diets for 52 weeks followed by a four-week recovery period on basal diet and sacrificed at 57 weeks, no uterine endometrial stromal polyps were observed.

In Table 5 OEHHA presents the incidence data as effective number (i.e., the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site), as well as findings from statistical tests conducted by OEHHA (i.e., Fisher’s exact pairwise test and Cochran-Armitage exact trend test). Tumor incidence data reported by US EPA (1997a) and findings from statistical tests conducted by US EPA (1997a) are presented in footnotes to Table 5.

As shown in Table 5, a significant increase in uterine endometrial stromal polyps was observed in the 400-ppm group with a dose-related trend using Fisher’s exact pairwise test and Cochran-Armitage exact trend test. Not all uteri were examined in the 1- and 60-ppm groups, and OEHHA acknowledges that due to selection bias in uterine tissue examination, the statistical tests conducted using the 1- and 60-ppm groups are likely biased. As explained in some detail in footnote 1 of Table 5, US EPA (1997a) reported a statistically significant increase in uterine endometrial stromal polyps in the 400-ppm group ($p = 0.044$), using Peto’s prevalence pairwise test, with a statistically significant trend using Peto’s prevalence trend test to analyze tumor incidence data from the control and 400-ppm groups expressed as effective number (i.e., the number of tumor bearing animals over the number of animals examined, excluding those that died or were sacrificed before observation of the first tumor, and excluding week 53 interim sacrifice animals). The discrepancy in uterine tumor incidence reported by OEHHA and US EPA (1997a) is also noted in that footnote.

The PWG did not re-evaluate the uterine histopathology slides from the Williams (1992) female SD rat study (US EPA 2020).

Table 5. Uterine tumor incidence in female SD rats exposed to ethoprop in the diet for 104 weeks, based on tumor identification by study pathologist (Williams 1992; US EPA 1997a)

Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test *p* value by OEHHA
	0	1	60	400	
	Daily dose (mg/kg/day)				
	0	0.06	3.56	23.98	
Endometrial stromal polyp[1] (313)	1/78	2/50	3/43	7/77*	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence and examined at the site (based on review of data reported in Williams (1992). Fisher's exact pairwise and Cochran-Armitage exact trend tests conducted by OEHHA. * $p < 0.05$. Daily doses in mg/kg/day from US EPA (2020).

[1] US EPA (1997a) stated that the uterine tumor incidence data for the 1- and 60-ppm groups were excluded from statistical analyses since not all uteri from animals in these groups were examined microscopically. US EPA (1997a) also stated that the 53-week interim sacrifice animals were excluded in the analyses. US EPA reported that there was a statistically significant increase (p = 0.044) in uterine endometrial stromal polyps in the 400-ppm group with incidence of 1/78 and 7/78 at 0 and 400 ppm, respectively, using Peto's prevalence test, also with a statistically significant trend using Peto's prevalence trend test (Table 6 in US EPA 1997a). US EPA (1997a) reports the incidence of these tumors in the 1- and 60-ppm groups as 2/52 and 3/44, respectively. The reason for the discrepancies between OEHHA and US EPA (1997a) in the incidence of these uterine tumors in the 1-, 60-, and 400-ppm dose groups is unclear.

Non-neoplastic findings

No dose-related increase in hyperplasia of the uterus was observed in female SD rats in the 104-week study.

Dose-dependent reductions in cholinesterase (plasma, red blood cell, and brain) activities were observed. At 104 weeks, plasma, red blood cell, and brain cholinesterase activities were reduced by 61, 39, and 32% in the 60-ppm group, and by 76, 41 and 66% in the 400-ppm group, reaching pairwise significance. Cholinesterase activities were also measured in the control and the 400-ppm group at week 57: plasma, red blood cell and brain activities were reduced by 20, 20 and 5% in the 400-ppm group compared to the controls.

4.1.2 105-week feeding studies in male and female F344 rats (Spicer 1985; US EPA 1997a, 2020; Hardisty 2017b)

105-week dietary studies in male and female F344 rats were conducted at the International Research and Development Corporation, Mattawan, Michigan from September 1982 to September 1984 (Spicer 1985, an unpublished study). The rats

were obtained from Charles River Laboratories, Inc. in Kingston, New York. Study reports were provided to the US EPA (US EPA 1997a, 2020).

Male and female F344 rats were administered ethoprop (purity 95.85%) in the diet at concentrations of 0, 1, 10, or 100 ppm, starting at six weeks of age, for 105 weeks. In these studies, each experimental group was comprised of 70 animals, with interim sacrifices of 10 animals per group at 52 and 79 weeks. The US EPA (2020) reported average daily doses of 0, 0.041, 0.40, and 4.19 mg/kg/day in males fed diets containing 0, 1, 10 and 100 ppm ethoprop respectively, and 0, 0.050, 0.515, and 5.12 mg/kg/day in females fed diets containing 0, 1, 10, and 100 ppm, respectively. Test diets were prepared by dissolving ethoprop in acetone and mixing with rodent chow; control diets consisted of rodent chow mixed with a comparable amount of acetone vehicle. All animals underwent necropsy with full tissue collection and histopathological examination. It was not reported whether the pathologist was aware of or blinded to the treatment status of the animals/tissues during histopathological examination.

Males

In males, survival in the dosed groups was not significantly different from the control group. Males at 10 ppm had higher body weights than controls, with statistically significant increases observed through most of weeks 2 through 87. In the 100-ppm group statistically significant decreases in body weight compared to controls were observed during weeks 1, 2, 5, and 6 and were attributed to reduced weight gain during the first treatment week. From weeks 64 to 104, the 100-ppm group had higher body weights compared to controls, reaching statistical significance at weeks 82 and 84. No treatment-related differences in food consumption were observed.

Tumors reported in Spicer (1985)

Tumors were observed in the thyroid and liver of male F344 rats in the 105-week study (Table 6). Statistically significant trends were observed in the incidence of thyroid C-cell[5] adenoma, carcinoma, and adenoma and carcinoma combined. The incidence of thyroid C-cell adenoma and carcinoma combined (15/47, 31.9%) in the 100-ppm group exceeded the historical control range for male F344/CrlBR rats from Charles River Laboratories, Inc. According to historical data compiled by Lang (1990), control ranges for 24-month studies conducted between 1980 and 1986 across 13 control groups were 0–14.3% for thyroid C-cell adenoma and 0–8.3% for medullary tumors (C-cell carcinoma). Statistically significant trends were also observed in the incidence of liver

[5] Thyroid C-cell tumors may also be referred to as thyroid medullary tumors, parafollicular cell tumors, and clear cell tumors (Spicer 1985; Lang 1990).

neoplastic nodules[6] (hepatocellular adenomas), and hepatocellular adenomas and carcinomas combined, although the liver tumor response was driven by hepatocellular adenomas. The incidence of hepatocellular adenomas in the 100-ppm group was 21.4% (9/42), above the Charles River historical control range (0–20.8%) for these tumors in male F344/CrlBR rats (Lang 1990). US EPA (1997a, 2020) did not mention the liver tumors observed in this male rat study.

No hepatocellular or thyroid C-cell tumors were observed at the 52- or 79-week interim sacrifices.

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

Table 6. Tumor incidence in male F344 rats administered ethoprop in the diet for 105 weeks, based on tumor identification by study pathologist (Spicer 1985; US EPA 1997a)

Tumor site	Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
		0	1	10	100	
		Daily dose (mg/kg/day)				
		0	0.041	0.4	4.19	
Thyroid	C-cell adenoma (675)	8/42	5/43	5/40	12/42	< 0.05
	C-cell carcinoma (611)	0/46	0/46	1/45	3/47	< 0.05
	C-cell adenoma and carcinoma (combined) (611)	8/46	5/46	6/45	15/47	< 0.01
Liver	Neoplastic nodule (hepatocellular adenoma) (657)	5/43	2/44	8/42	9/42	< 0.05
	Hepatocellular carcinoma (675)	1/42	1/43	0/40	1/42	NS
	Hepatocellular adenoma and carcinoma (combined) (657)	6/43	3/44	8/42	10/42	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site (based on review of data reported in Spicer (1985)). Fisher's exact pairwise and exact trend tests conducted by OEHHA. NS: not significant. Daily doses in mg/kg/day from US EPA (2020).

PWG re-evaluation of Spicer (1985) male rat thyroid C-cell tumors (Hardisty 2017b)

A PWG organized by the registrant, AMVAC Chemical Corporation, re-evaluated the histopathology of the thyroid C-cell tumors in the Spicer (1985) male F344 rat study (Hardisty 2017b, an unpublished study), and the US EPA accepted the findings of that re-evaluation (US EPA 2020). Table 7 presents the thyroid C-cell tumor incidence based on the PWG re-evaluation, using information reported in Hardisty (2017b). Analyzing these data, statistically significant trends in the incidence of thyroid C-cell adenoma, carcinoma, and adenoma and carcinoma combined were observed, with a statistically significant increase in thyroid C-cell adenoma and carcinoma combined in the high-dose group, by pairwise comparison with controls.

Table 7. Incidence of thyroid C-cell tumors in male F344 rats administered ethoprop in the diet for 105 weeks (Spicer 1985), based on tumor identification by the PWG re-evaluation (Hardisty 2017b; US EPA 2020[1])

Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
	0	1	10	100	
	Daily dose (mg/kg/day)				
	0	0.041	0.4	4.19	
C-cell adenoma (695)	5/39	4/42	5/38	11/42	< 0.05
C-cell carcinoma (611)	1/46	0/46	1/45	4/47	< 0.05
C-cell adenoma and carcinoma (combined) (611)	5/46	4/46	6/45	15/47*	< 0.001

Incidence based on data reported in the 2017 PWG re-evaluation (Hardisty 2017b) of the thyroid histopathology findings of Spicer (1985). Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site. Exact trend test and Fisher's exact pairwise test conducted by OEHHA. * $p < 0.05$ for pairwise comparison with control.

[1] US EPA (2020, Table 12) reported different tumor counts than the PWG re-evaluation (Hardisty, 2017b): adenoma 5/59, 3/56, 5/60, 12/60 (trend $p < 0.01$); carcinoma 1/59, 0/56, 1/60, 3/60 (trend $p = 0.0677$); combined 5/59, 3/56, 6/60, 15/60 (trend $p < 0.01$; pairwise at 100 ppm $p < 0.05$). The reason for the discrepancy in tumor counts between Hardisty (2017b) and US EPA (2020) is unclear. US EPA (2020, Table 12) presents the tumor incidence data as "the number of tumor bearing animals over the number of animals examined excluding those that died or were sacrificed before week 54."

Non-neoplastic findings

In male rats a dose-related inhibition of cholinesterase activity was observed in treated animals, compared to controls. At 10 ppm, plasma cholinesterase was reduced to 71–40% of control values and red blood cell (RBC) cholinesterase was reduced to 95–86% of control values. At 100 ppm, plasma cholinesterase was reduced to 29–13% of control values, RBC cholinesterase was reduced to 65–55% of control values, and brain cholinesterase was reduced to 73–65% of control values.

No treatment-related clinical observations or cholinergic signs of toxicity were reported.

Females

In females, survival in the dosed groups was not significantly different from the control group. Mean body weights in the 1- and 10-ppm groups were comparable to controls throughout the study. In the 100-ppm group, statistically significant decreases were

observed at weeks 1, 2, 3, 5, and 6, after which body weights were comparable to controls. No treatment-related differences in food consumption were observed.

Tumors reported in Spicer (1985)

Tumors were observed in the thyroid and pancreas of female F344 rats in the 105-week study (Table 8). A statistically significant positive trend was observed in the incidence of combined thyroid C-cell adenomas and carcinomas. Two pancreatic islet cell adenomas were observed in females at 100 ppm, with none in the control, 1-ppm, or 10-ppm groups (Table 8). This tumor type is uncommon in female F344 rats (Koivisto et al. 2012). US EPA (1997a, 2020) did not mention the uncommon pancreatic tumors observed in this female rat study.

No thyroid C-cell or pancreatic islet cell tumors were observed at the 52-week interim sacrifice. One thyroid adenoma was observed at 100 ppm at the 79-week interim sacrifice.

Table 8. Tumor incidence in female F344 rats administered ethoprop in the diet for 105 weeks, based on tumor identification by study pathologist (Spicer 1985; US EPA 1997a)

Tumor site	Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
		0	1	10	100	
		Daily dose (mg/kg/day)				
		0	0.05	0.515	5.12	
Thyroid	C-cell adenoma (549)	2/59	4/58	0/55	6/59	NS
	C-cell carcinoma (735)	0/40	1/40	0/41	1/42	NS
	C-cell adenoma and carcinoma (combined) (549)	2/59	5/58	0/55	7/59	< 0.05
Pancreas	Islet cell adenoma (736)	0/40	0/40	0/41	2/42	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first tumor occurrence and examined at the site. Fisher's exact pairwise and exact trend tests conducted by OEHHA. NS: not significant. Daily doses in mg/kg/day from US EPA (2020).

PWG re-evaluation of Spicer (1985) female rat thyroid C-cell tumors (Hardisty 2017b)

The PWG re-evaluated the histopathology of the thyroid C-cell tumors in the Spicer (1985) female F344 rat study (Hardisty 2017b), and the US EPA accepted the findings of that re-evaluation (US EPA 2020). Table 9 presents the thyroid C-cell tumor incidence based on the PWG re-evaluation, using information reported in Hardisty (2017b). Analyzing these data, there were no statistically significant trends or increases in thyroid C-cell tumors in treated compared to control animals.

Table 9. Incidence of thyroid C-cell tumors in female F344 rats administered ethoprop in the diet for 105 weeks (Spicer 1985), based on tumor identification by the PWG re-evaluation (Hardisty 2017b; US EPA 2020)

Tumor type (day of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
	0	1	10	100	
	Daily dose (mg/kg/day)				
	0	0.05	0.515	5.12	
C-cell adenoma (549)	1/59	3/58	0/55	4/59	NS
C-cell carcinoma (737)	0/40	0/40	1/41	0/42	NS
C-cell adenoma and carcinoma (combined) (549)	1/59	3/58	1/55	4/59	NS

Incidence based on data reported in the 2017 PWG re-evaluation (Hardisty 2017b) of the thyroid histopathology of Spicer (1985). Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site. Fisher's exact pairwise and exact trend tests conducted by OEHHA. NS: not significant.

Non-neoplastic findings

Hyperplasia was observed in the pancreas in treated female rats. The incidence of hyperplasia was 4/70, 1/70, 0/70 and 7/70 in the control, 1-ppm, 10-ppm, and 100-ppm groups, respectively. These increases did not reach statistical significance by pairwise comparison with controls but did have a significant trend ($p = 0.01$).

In female rats a dose-related inhibition of cholinesterase was observed in treated animals, compared to controls. At 10 ppm, plasma cholinesterase was reduced to 46–38% of control values and RBC cholinesterase was reduced to 96–73% of control values. At 100 ppm, plasma cholinesterase was reduced to 7–6% of control values, RBC cholinesterase was reduced to 72–52% of control values, and brain cholinesterase was reduced to 64–52% of control values.

No treatment-related clinical observations or cholinergic signs of toxicity were reported.

4.1.3. Feeding studies in male and female F344 rats exposed via parental exposure preconception, maternal exposure in utero and during lactation, and direct exposure in the diet from weaning to 112 weeks of age (Barnett et al 1983; US EPA 1997a, 2020).

Feeding studies in male and female F344 rats were conducted at the New Iberia, Louisiana facility of the Gulf South Research Institute (GSRI) (Barnett et al. 1983, an unpublished study).[7,8] These studies included dietary exposures in F_0 parental rats preconception, and *in utero*, lactational, and dietary exposures (from weaning to 112 weeks of age) in F_1 rats. The parental animals were obtained from the Charles River Breeding Laboratories. Study reports were provided to the US EPA (US EPA 1997a, 2020).

Male (n = 80) and female (n = 175) weanling breeder parental (F_0) F344 rats were administered ethoprop (purity 95.3%) in the diet at concentrations of 0, 60.5, 131, or 262 ppm. Ethoprop-containing feed was prepared twice weekly, with ethoprop first dissolved in corn oil and then mixed into the feed to produce the desired concentrations. F_0 animals were housed individually during an eight-week premating exposure period, after which two females were paired with one male for mating. Males were removed after sperm-positive status was confirmed, and females in each dose group were then fed diets containing reduced concentrations of ethoprop, as follows: control (0 ppm), low

[7] The Barnett et al. (1983) studies on ethoprop were conducted from June 1977 to December 1979. The quality of studies conducted by GSRI in the 1980s was called into question, including several studies performed under contract with the National Toxicology Program (NTP), as outlined below. However, studies conducted by GSRI prior to 1980 were not called into question, including the ethoprop studies of Barnett et al. (1983), where the “in life” portions of the studies were completed in December 1979. Importantly, in 1979 the US General Accounting Office (US GAO) evaluated GSRI’s testing conditions as good overall with some deficiencies (pathologists not having all necessary data on the animal conditions while reviewing slides, animals killed by improper chemical dosing techniques being designated as "natural" death, and temperature or humidity alarms not functioning properly). The US GAO reported that GSRI “stated that it had made changes in both its operations and facilities to correct the deficiencies” (US GAO 1979). NTP subsequently published reports for three sets of studies GSRI was contracted to conduct during 1977-1979, which is the same time during which GSRI conducted the Barnett et al. studies. In 1984, NTP raised further concerns regarding GLP [good laboratory practice] compliance, pathology analysis, and data-tracking in the bioassays conducted by GSRI in the early 1980s. NTP subsequently terminated its contractual relationship with GSRI. While Barnett et al. (1983) was not criticized, and OEHHA did not identify any concerns or evidence related to the issues raised by NTP in 1984, we cannot rule out the possibility that Barnett et al. could have suffered from some of the serious flaws encountered in subsequent GSRI studies.

[8] US General Accounting Office (GAO) (1979). Letter to Henry A Waxman March 30, 1979. United States General Accounting Office. https://www.gao.gov/assets/hrd-79-51.pdf Accessed: June 15, 2026

dose (4.5 ppm), mid dose (9 ppm), and high dose (18 ppm) throughout gestation and lactation, until weaning of the pups. At birth, litters were culled to eight offspring, with a preferred distribution of four males and four females per litter. At weaning at 21 days of life, offspring from each litter were allocated to dose groups of 60 F_1 animals/sex, keeping the same dose assigned to the dam during gestation and lactation (e.g., 0, 4.5, 9, or 18 ppm). F_1 animals were fed diets containing ethoprop at 0, 4.5, 9, or 18 ppm at weaning, designated as "week 0" of the study, and through "week 12" of the study in both males and females. At "week 13" of the study, the F_1 male and female rats were fed diets containing increased concentrations of ethoprop, as follows: control (0 ppm), low dose (49 ppm), mid dose (98 ppm), and high dose (196 ppm) until conclusion of the studies at "week 109". Interim sacrifices of 10 F_1 animals/group were conducted at "week 52" in the male and female studies. F_0 males were sacrificed after mating and F_0 females were sacrificed after offspring production and weaning, and no pathology analysis of F_0 animals was conducted. All animals in the F_1 male and F_1 female studies underwent necropsy and gross examination. The liver, kidneys, heart, testes or ovary and uterus, thyroid, spleen, and adrenals were dissected during interim sacrifice. At final sacrifice, moribund or found dead animals, all major organs of each animal underwent histopathology examination. It was not reported whether the pathologist was aware of or blinded to the treatment status of the animals/tissues during histopathological examination.

OEHHA identified flaws in the reporting of the weekly observations and inconsistences in the data tables in Barnett et al. (1983) and was able to address these issues by reviewing the detailed animal data provided in appendices. OEHHA noted these observations and interpretations in the tumor incidence tables below.

Males

In F_1 males, survival rates were comparable across groups and declined over time. One exception was a statistically significant 13.5% decrease in survival at study week 48, in the 196-ppm group compared to control ($p < 0.01$); no statistically significant differences in survival were reported throughout the remainder of the study for any treated group. Body weights were statistically significantly reduced ($p < 0.05$) in the 98- and 196-ppm groups compared to controls for the majority of the study period. In the 196-ppm group, significant reductions in body weight began as early as study week 0 (weaning) and ranged from 10.4 to 17.3% below control weights for the duration of the study. In the 98-ppm group significant reductions in body weight were observed as early as week 2 and ranged from 0.4 to 11.3% below control weights for the duration of the study. Food consumption was also statistically significantly decreased in the 98-ppm and 196-ppm groups compared to controls.

Tumors were observed in the thyroid of male F_1 F344 rats in the Barnett et al. (1983) study (Table 10). A statistically significant increase in thyroid C-cell adenomas was observed in the 196-ppm group, with a statistically significant dose-related trend. No historical control data on thyroid C-cell tumors were reported in Barnett et al. (1983).

No thyroid C-cell tumors were observed at the "week 52" interim sacrifice.

Table 10. Incidence of thyroid gland tumors in male F344 rats exposed via parental exposure preconception, *in utero* and lactational exposures, and direct exposure in the diet from weaning to 112 weeks of age (Barnett et al. 1983)

Tumor type (week of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
	0	49	98	196	
	Daily dose (mg/kg/day)[1]				
	0	0.94	2.47	4.74	
C-cell adenoma (93)	2/45	4/45	1[2]/34	10/39**	< 0.01

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site. Week of first tumor is based on review of data reported in Table 38 in Barnett et al. (1983). Fisher's exact pairwise and exact trend tests conducted by OEHHA. ** $p < 0.01$ for pairwise comparison with control.

[1] The daily doses shown here correspond to the administered doses from study week 13 to study termination. From study week 0 to week 12, concentrations in feed were 0, 4.5, 9, or 18 ppm with an average daily dose of 0, 0.19, 0.39 or 0.73 mg/kg/day, respectively. Daily doses in mg/kg/day were reported in Table 7 of Barnett et al. (1983).

[2] There was an apparent error in recording the time of death of this tumor-bearing animal MM-34: death was reported at "week 23" in the weekly observations (Barnett et al. (1983) Volume III, page 248) and it was also listed as a terminal sacrifice in the pathology report. Data on this rat (weekly body weight and food consumption) was recorded throughout the study duration until "week 109" (Volume II appendices VII and IX). Thus, it was interpreted that this animal died at study termination rather than at study week 23.

Non-neoplastic findings

In male rats, cholinesterase activity decreased significantly ($p < 0.05$) in the plasma and brain. Plasma cholinesterase activity reported for males was 81%, 84%, and 86% of control levels for the 49-, 98-, and 196-ppm groups, respectively, and brain cholinesterase activity was 45% and 78% of control levels for the 98- and 196-ppm groups, respectively.

In the 196-ppm group, emaciation and poor grooming were observed.

Females

In F_1 females, survival rates were comparable across groups and declined over time with no statistically significant differences compared to control at the end of the study

reported for any group. Body weights were statistically significantly reduced ($p < 0.05$) in the 196-ppm group for the majority of the study period. Significant reductions began as early as week 4 of the study and ranged from 10.1 to 16% below control weights. Food consumption decreased for substantive periods of time in each treatment group; a statistically significant reduction in food consumption was observed in the 49-ppm group for a total of 36 weeks, in the 98-ppm group for 53 weeks, and in the 196-ppm group for 60 weeks.

Tumors were observed in the uterus of female F_1 Fisher 344 rats in the Barnett et al. (1983) study (Table 11). A statistically significant increase in endometrial polyps in the 98- and 196-ppm groups was reported with a significant dose-related trend. The combined incidence of endometrial and stromal polyps was also statistically significant by Fisher's exact pairwise test in the 196-ppm group and by exact trend test. Endometrial adenomas and adenocarcinomas were also observed, and a statistically significant dose-related trend was observed for the combined incidence of endometrial adenoma and adenocarcinoma.

Endometrial and stromal polyps are considered common lesions in F344 rats. Endometrial adenomas and adenocarcinomas are considered rare in most rat strains including the F344 strain (Dixon et al. 2018; Nagaoka et al. 1990; Solleveld et al. 1984). No historical control data were reported by Barnett et al. (1983).

No uterine tumors were observed at the "week 52" interim sacrifice.

Table 11. Incidence of uterine tumors in female Fisher 344 rats exposed via parental exposure preconception, *in utero* and lactational exposures, and direct exposure in the diet from weaning to 112 weeks of age (Barnett et al. 1983)

Tumor type (week of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
	0	49	98	196	
	Daily dose (mg/kg/day)[1]				
	0	1.24	2.91	5.91	
Stromal polyp (87)	8/45	2/46	2/47	3/44	NS
Endometrial polyp (109)	0/34	4/40	8/36**	13/32***	< 0.001
Endometrial and stromal polyps[2] (combined) (87)	8/45	6/46	10/47	16/44*	< 0.01
Endometrial adenoma [rare][3] (99)	0/40	0/43	0/40	2/41	NS
Endometrial adenocarcinoma [rare][3] (105)	1/36	0/42	0/37	2/35	NS
Endometrial adenoma and adenocarcinoma (combined) [rare][3] (99)	1/40	0/43	0/40	4/41	< 0.05

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site. Week of first tumor based on review of data reported in Table 39 in Barnett et al. (1983). Fisher's exact pairwise and exact trend tests conducted by OEHHA. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NS: not significant.

[1] The daily doses shown here correspond to the administered doses from study week 13 to study termination. From study week 0 to 12, concentrations in feed were 0, 4.5, 9, or 18-ppm with an average daily dose of 0, 0.23, 0.49 or 0.97 mg/kg/day, respectively. Daily doses in mg/kg/day were reported in Table 7 of Barnett et al. (1983).

[2] Endometrial and stromal polyps are commonly designated as a single tumor type "endometrial stromal polyp" (Dixon et al. 2018). However, in Barnett et al. (1983), the tumors are reported as either endometrial polyps or stromal polyps. OEHHA therefore presents both the separate and combined incidences, based on the individual animal data reported in Barnett et al. (1983).

[3]Endometrial adenomas and adenocarcinomas are rare tumors in F344 rats (Dixon et al. 2018; Nagaoka et al. 1990; Solleveld et al. 1984).

Non-neoplastic findings

Hyperplasia was observed in the thyroid gland in treated female rats. The incidence of thyroid C-cell hyperplasia was 0/50, 3/50, 3/50 and 4/50 in the control, 49-, 98-, and

196-ppm groups, respectively. These increases did not reach statistical significance by pairwise comparison with controls or by the test for trend.

In female rats, cholinesterase activity decreased significantly ($p < 0.05$) in plasma and brain. Plasma cholinesterase activity reported for females was 89%, 91% and 93% of control levels in the 49-, 98-, and 196-ppm groups, respectively, and brain cholinesterase activity was 30, 50% and 65% of control levels in the 49-, 98-, and 196-ppm groups, respectively.

In the 196-ppm group, emaciation and poor grooming were observed.

4.2 Carcinogenicity Studies of Ethoprop in Mice

4.2.1 104-week feeding studies in male and female B6C3F$_1$ mice (Inoue 1984; US EPA 1997a)

104-week dietary studies in male and female B6C3F$_1$ mice were conducted by the Biosafety Research Center, Foods, Drugs and Pesticides (An-Pyo Center), Shizuoka-ken, Japan (Inoue 1984, an unpublished study), and study reports were provided to the US EPA (US EPA 1997a).

Male and female specific pathogen free (SPF) B6C3F$_1$ mice were administered ethoprop (purity 94.6%) in the diet starting at 5 weeks of age at concentrations of 0, 0.2, 2, and 30 ppm for 104 weeks. In these studies, each experimental group was comprised of 80 animals, with interim sacrifices of 10 animals per group at 26, 52 and 78 weeks. Average daily doses were reported to be 0, 0.032, 0.306, and 4.66 mg/kg/day in males for the 0-, 0.2-, 2-, and 30-ppm groups, respectively and 0, 0.038, 0.381, and 5.90 mg/kg/day in females for the 0-, 0.2-, 2-, and 30-ppm groups, respectively (Inoue 1984). Test diets were prepared by incorporating ethoprop into basal animal diet on a weight-per-weight basis, with 2% olive oil added as a dust suppressant, while control diets were prepared using the same procedure but without ethoprop. All animals underwent gross necropsy and full histopathological examination, except animals in interim sacrifice groups, for which only selected tissues were included in the histopathological examination. It was not reported whether the pathologist was aware of or blinded to the treatment status of the animals/tissues during histopathological examination.

Males

No treatment related effects on survival were observed in males until week 98, when a statistically significant decrease was observed at 0.2 ppm compared to controls. At 0.2 ppm, body weights were comparable to controls for most of the study, with isolated significant reductions observed at weeks 32, 36, 66, and 70–88. At 2 ppm, weights

remained near control levels during the early months of the study and showed significant reductions intermittently at weeks 28, 30, 36, 48–54, 72, and 78. At 30 ppm, a consistent and sustained significant reduction in body weights compared to controls was observed from week 1 through week 90. No treatment-related differences in food consumption were observed.

No statistically significant increases in tumors were observed at any site in ethoprop-treated males. Tumors were observed in the liver (Table 12), including non-significant increase in the incidence of hepatocellular carcinoma at 0.2 ppm and non-significant increases in hepatocellular adenoma, and adenoma and carcinoma combined in the 0.2- and 2-ppm groups.

Table 12. Incidence of liver tumors in male B6C3F$_1$ mice administered ethoprop in the diet for 104 weeks (Inoue 1984)

Tumor Type (week of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
	0	0.2	2	30	
	Daily dose (mg/kg/day)				
	0	0.032	0.306	4.66	
Hepatocellular adenoma (52)	13/70	12/70	17/70	12/70	NS
Hepatocellular carcinoma (52)	5/70	11/70	4/70	5/70	NS
Hepatocellular adenoma and carcinoma (combined) (52)	16/70	22/70	21/70	16/70	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first tumor occurrence and examined at the site. Fisher's exact pairwise and exact trend test conducted by OEHHA. NS: not significant.

Non-neoplastic findings

In male mice a dose-related inhibition of cholinesterase was observed in treated animals, compared to controls. At 2 ppm, plasma cholinesterase was reduced to 76–65% of control values across weeks 26, 52, and 78, and RBC cholinesterase was reduced to 87–88% of control values at weeks 52 and 78. At 30 ppm, plasma cholinesterase was reduced to 34–23% of control values, RBC cholinesterase was reduced to 23–19% of control values, and brain cholinesterase was reduced to 89–64% of control values at weeks 26, 52, 78, and 104.

No treatment-related clinical observations or cholinergic signs of toxicity were reported.

Females

In females, survival in the dosed groups was not significantly different from the control group, although at terminal sacrifice survival in the 0.2-ppm group (72%) was lower than controls (75%), and survival in the 2- and 30-ppm groups (86% in each) was higher than controls. In the 0.2-ppm group, mean body weight was significantly decreased compared to controls from weeks 36 to 78. In the 2-ppm group, significant reductions in mean body weights compared to controls were observed in weeks 1 to 3 and weeks 6 to 9. At 30 ppm, body weights were significantly lower than controls from weeks 1 to 80 and recovered to control levels by the end of the study. No treatment-related differences in food consumption were observed.

Tumors were observed in the liver of female $B6C3F_1$ mice in the 104-week study (Table 13), including four hepatocellular adenomas in the 78-week interim sacrifice groups (two in controls, one in the 0.2-ppm group, and one tumor in the 2-ppm group. No hepatocellular tumors were observed in the 26- or 52-week interim sacrifice groups. A statistically significant trend was observed in the incidence of hepatocellular carcinomas, but not in the incidence of hepatocellular adenomas and carcinomas combined. The incidence of hepatocellular carcinoma in the 30-ppm group (9/59, 15.3%) exceeded the laboratory historical control rate of 6.5% (74/1,130) reported by Hirouchi et al. (1994) from the An-Pyo Center over a 12-year period (1980–1992). US EPA (1997a) did not consider the observed hepatocellular tumors to be treatment-related, as no pairwise comparison with concurrent controls reached statistical significance.

Table 13. Incidence of liver tumors in female $B6C3F_1$ mice administered ethoprop in the diet for 104 weeks (Inoue 1984; US EPA 1997a[1])

Tumor Type (week of first tumor)	Administered concentration (ppm)				Cochran-Armitage exact trend test p value by OEHHA
	0	0.2	2	30	
	Daily dose (mg/kg/day)				
	0	0.038	0.381	5.9	
Hepatocellular adenoma (78)	7/59	4/57	8/60	4/58	NS
Hepatocellular carcinoma (77)	4/59	3/57	1/60	9/59	< 0.01
Hepatocellular adenoma and carcinoma (combined) (77)	11/59	7/57	9/60	13/59	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first tumor occurrence and examined at the site. Fisher's exact pairwise and exact trend test conducted by OEHHA. NS: not significant.

[1] In reporting liver tumor incidences for this study, US EPA (1997a) excluded animals that died or were sacrificed before week 53 and did not include tumors observed at interim sacrifice. Specifically, US EPA reported the following: hepatocellular adenoma (5/49, 2/49, 7/50, 4/49; trend NS); hepatocellular carcinoma (4/49, 3/49, 1/50, 9/49; trend $p < 0.01$); hepatocellular adenoma/carcinoma combined (9/49, 5/49, 8/50, 13/49; trend $p < 0.05$).

Non-neoplastic findings

In female mice a dose-related inhibition of cholinesterase was observed in treated animals, compared to controls. At 2 ppm, plasma cholinesterase was reduced to 90–79% of control values at weeks 26, 52, 78, and 104, and RBC cholinesterase was reduced to 87% and 83% at weeks 26 and 78, respectively. At 30 ppm, plasma cholinesterase was reduced to 36–28% of control values, RBC cholinesterase was reduced to 26–21% of control values, and brain cholinesterase was reduced to 90–71% of control values at weeks 26, 52, and 104.

No treatment-related clinical observations or cholinergic signs of toxicity were reported.

4.3 Summary of Animal Carcinogenicity Studies of Ethoprop

Evidence for the carcinogenicity of ethoprop comes from long-term carcinogenicity studies in rodents of both sexes. Tumors were observed in animals exposed to ethoprop in the diet (three studies in rats and one in mice) and in two studies in rats exposed via feed with exposure preconception, *in utero* and via lactation. A bulleted summary of the animal tumor findings is presented below by study, sex, strain and species.

4.3.1 OEHHA's summary of tumor findings

Tumors in male SD rats in a 104-week feeding study (Williams 1992)

- A statistically significant increase in the incidence of adrenal malignant pheochromocytoma was observed in the 1-ppm group.
- The incidence of thyroid C-cell carcinoma, and thyroid C-cell adenoma and carcinoma (combined) showed statistically significant dose-related trends.
- A statistically significant increase in the incidence of thyroid follicular cell adenoma was observed in the 400-ppm group.

Tumors in female SD rats in a 104-week feeding study (Williams 1992)

- A statistically significant increase in the incidence of uterine endometrial stromal polyps was observed in the 400-ppm group, with a statistically significant dose-related trend.

Tumors in male F344 rats in a 105-week feeding study (Spicer 1985)

- The incidences of thyroid C-cell adenoma, carcinoma, and adenoma and carcinoma (combined) showed statistically significant dose-related trends. A statistically significant increase in the incidence of thyroid C-cell adenoma and carcinoma (combined) was observed in the 100-ppm group.
- The incidences of hepatocellular adenoma, and hepatocellular adenoma and carcinoma (combined) showed statistically significant dose-related trends.

Tumors in female F344 rats in a 105-week feeding study (Spicer 1985)

- Two pancreatic islet cell adenomas were observed in the 100-ppm dose group, with none observed in the control or two lower dose groups. This lesion is considered uncommon in female F344 rats.

Tumors in F_1 male F344 rats in a lifetime feeding study with exposure preconception, *in utero* and via lactation (Barnett et al. 1983)

- A statistically significant increase in the incidence of thyroid C-cell adenoma was observed in the 196-ppm group, with a statistically significant dose-related trend.

Tumors in F_1 female F344 rats in a lifetime feeding study with exposure preconception, *in utero* and via lactation (Barnett et al. 1983)

- The incidence of endometrial adenoma and adenocarcinoma (combined) showed a statistically significant trend. Endometrial adenoma and adenocarcinoma are considered rare tumors in the F344 rat.
    - Two rare endometrial adenomas were observed in the 196-ppm dose group, with none observed in the control or two lower dose groups.
    - Two rare endometrial adenocarcinomas were observed in the 196-ppm dose group, with one observed in the control and none observed in the two lower dose groups.
- Statistically significant increases in uterine endometrial polyp were observed in 98- and 196-ppm dose groups, with a statistically significant dose-related trend. A statistically significant increase in endometrial polyp and stromal polyp (combined) was observed in the 196-ppm group, with a statistically significant dose-related trend.

Tumors in female $B6C3F_1$ mice in a 104-week feeding study (Inoue 1984)

- The incidence of liver hepatocellular carcinoma showed a statistically significant trend.

The statistically significant findings described above are presented in Table 14, below, along with statistically significant findings identified by the US EPA in 1997a and 2020.

Table 14. Statistically significant tumor findings identified by the US EPA in 1997a and 2020 and by OEHHA[1]

Sex	Tumor site	Tumor type	US EPA 1997a		US EPA 2020		OEHHA	
			Pairwise	Trend	Pairwise	Trend	Pairwise	Trend
SD rat (Williams 1992)[2]								
M	**Adrenal gland**	Malignant pheochromocytoma	400 ppm	Y	1 ppm	N	1 ppm	N
	Thyroid gland	C-cell carcinoma	400 ppm	Y	N	Y	N	Y
		C-cell adenoma and carcinoma (combined)	N	N	N	N	N	Y
		Follicular cell adenoma	1, 60, 400 ppm	N	NC	NC	400 ppm	N
		Follicular cell adenoma and carcinoma (combined)	400 ppm	N			N	N
F	**Uterus**	Endometrial stromal polyp	400 ppm	Y	NC	NC	400 ppm	Y
F344 rat (Spicer 1985)								
M	**Thyroid gland**	C-cell adenoma	N	Y	N	Y	N	Y
		C-cell carcinoma	N	Y	N	N	N	Y
		C-cell adenoma and carcinoma (combined)	N	Y	100 ppm	Y	100 ppm	Y
	Liver	Hepatocellular adenoma	NC	NC	NC	NC	N	Y
		Hepatocellular carcinoma	NC	NC	NC	NC	N	N
		Hepatocellular adenoma and carcinoma (combined)	NC	NC	NC	NC	N	Y
F344 rat (Barnett et al. 1983)[3]								
M	**Thyroid gland**	C-cell adenoma	196 ppm	Y	NC	NC	196 ppm	Y

Sex	Tumor site	Tumor type	US EPA 1997a		US EPA 2020		OEHHA	
			Pairwise	Trend	Pairwise	Trend	Pairwise	Trend
F	**Uterus**	Endometrial polyp	98, 196 ppm	Y	NC	NC	98, 196 ppm	Y
		Endometrial and stromal polyp (combined)	196 ppm	Y			196 ppm	Y
		Endometrial adenoma and adenocarcinoma (combined) [rare][4]	N	N			N	Y
B6C3F$_1$ mouse (Inoue 1984)								
F	**Liver**	Hepatocellular carcinoma	N	Y	NC	NC	N	Y
		Hepatocellular adenoma and carcinoma (combined)	N	Y			N	N

[1] Statistically significant tumor findings across dosed groups were calculated using Fisher's exact pairwise test (denoted as "Pairwise"). Trends were determined using the exact trend test (denoted as "Trend"). US EPA (2020) and OEHHA re-analyzed adrenal gland tumors in SD rats, and thyroid C-cell tumors in SD and F344 rats (Williams 1992; Spicer 1985) based on the PWG (Hardisty 2017a, b) re-evaluation.

[2] For the SD rat data, Peto's prevalence tests were used for both pairwise comparisons and trend analyses as reported by US EPA (1997a; 2020).

M, male; F, female; Y, significant by trend ($p < 0.05$); N, not significant; NC, not considered

[3] Exposure in this study included parental exposure preconception, maternal exposure *in utero* and during lactation, and direct exposure in the diet after weaning. US EPA (1997a) considered Barnett et al. (1983) as a "supplementary study."

[4] Two endometrial adenomas were observed in the 196-ppm group with none observed in the control or lower dose groups. Two endometrial adenocarcinomas were observed in the 196-ppm group with one observed in the control and none observed in the lower dose groups. Both endometrial adenomas and adenocarcinomas are considered rare tumors (Dixon et al. 2018; Nagaoka et al. 1990; Solleveld et al. 1984).

5. MECHANISTIC CONSIDERATIONS AND OTHER RELEVANT DATA

5.1 Pharmacokinetics and Metabolism

5.1.1 Overview

Data relevant to the absorption, distribution, metabolism, and elimination (ADME) of ethoprop in humans are available from one study in agricultural applicators (Lunchick et al. 2005) and one unpublished *in vitro* study of excised human skin (Stoughton 1986). Data are also available from *in vivo* and *in vitro* studies conducted in animals. Specifically, studies have been conducted *in vivo* in rats (Iqbal and Menzer 1972; Yenne 1990, unpublished study) and zebrafish (Grasse et al. 2024) and *in vitro* with rat and rabbit microsomes (Iqbal and Menzer 1972) and mouse, rat, and rabbit skin (Stoughton 1986).

Ethoprop appears to be readily absorbed and rapidly metabolized in occupationally exposed humans. It is also readily absorbed in rats and mice exposed by the oral route and in zebrafish embryos incubated in the presence of ethoprop. Ethoprop can also be absorbed through the skin, as demonstrated in *in vitro* studies of excised human, rat, mouse, and rabbit skin (Stoughton 1986). Once absorbed, ethoprop enters the bloodstream, is distributed throughout the body, and rapidly metabolized. Ethoprop is metabolized primarily through de-propylation, with O-de-ethylation also occurring. Ethoprop does not accumulate in the body. Ethoprop is largely excreted in urine; feces and expired air are secondary routes of elimination.

5.1.2 Absorption

A study of agricultural applicators provides information indicating that humans can absorb ethoprop (Lunchick et al. 2005). Twenty workers performing a total of 23 replicates (three of the workers were monitored more than once) of mixing, loading, or applying ethoprop to potato fields across 13 sites in south-central Washington state wore personal air samplers to measure airborne concentrations of ethoprop for inhalation exposure estimation. To assess absorbed dose, urine was collected and pooled for the 24-hour period prior to the initiation of the study, and, starting on the first day of study initiation (i.e., the day of ethoprop mixing–loading–application), for 12-hour intervals over the course of four days. Nine of the workers were occupationally exposed to ethoprop on the first day only, and 11 were exposed for two or three days. Urine samples were analyzed for ethoprop and one ethoprop metabolite, O-ethyl S-propyl phosphorothioate. The publication did not present data on the levels of ethoprop (or its metabolite) measured in either the personal air or urine samples. The authors reported

that ethoprop was not detected in any of the urine samples (DL: 0.0016 µg/mL), and that the ethoprop metabolite, O-ethyl S-propyl phosphorothioate, was detected in urine (DL: 0.0046 µg/mL). Among those workers only exposed on the first day of the study, the ethoprop metabolite was not detected in urine after the first 24 hours, indicating rapid metabolism and excretion.

Evidence in animals that ethoprop is absorbed by the oral route includes findings from studies of radiolabeled ethoprop administered by gavage or in drinking water to rats (Iqbal and Menzer 1972; Yenne 1990, an unpublished study), as well as observations of treatment-related effects following dietary administration of ethoprop in the rat and mouse carcinogenicity studies discussed in Section 4. The studies conducted in rats with radiolabeled ethoprop by Iqbal and Menzer (1972) and Yenne (1990) demonstrated that ethoprop is rapidly and completely absorbed by the oral route. In Iqbal and Menzer (1972), O-ethyl-^{14}C or S-propyl-^{14}C labeled ethoprop administered to rats by oral gavage or in drinking water was absorbed and completely metabolized within six hours. Yenne (1990) observed peak presence of radioactivity in blood within 30–42 minutes (T_{max}) of oral gavage of a single dose of ^{14}C-labeled ethoprop (4 or 12.5 mg/kg-bw in females; 4 or 25 mg/kg-bw in males), with the level of radioactivity gradually declining over the next 24 hours.

Dermal absorption was examined by Stoughton (1986; unpublished study) using an *in vitro* skin penetration system. Fresh skin specimens were obtained from Swiss Webster mice, white laboratory rats, mature albino rabbits, and human cadavers (mid-abdominal region); all subcutaneous fat of the skin was removed. C^{14}-labeled ethoprop was applied as 0.02 mL of either the undiluted 70% emulsified concentrate or a 1:19 dilution in distilled water to the epidermal surface of each specimen. Saline aliquots were collected at 15 minutes, 30 minutes, 1, 2, 4, 6, and 24 hours post-application and assayed for radioactivity by liquid scintillation counting. Results showed ethoprop absorption across all samples. Ethoprop absorption was higher when delivered as a dilution, and a lag phase was observed for all species within the first hour followed by a near constant rate of penetration for the next 23 hours. The amount of applied dose penetrating the skin after 24 hours ranged from 1 to 5.2% for human skin, 5.4 to 22.6% for rat skin, 7.84 to 27.4% for rabbit skin, and 16.2 to 37.8% for mouse skin.

In the study by Grasse et al. (2024), zebrafish embryos (*Danio rerio*) were exposed to ethoprop (ethoprophos) for 96 hours starting at 4 ± 1 hours post-fertilization at a single sublethal concentration (10- to 100-fold below the lethal dose for 50% of the test population, or LC_{50}). Ethoprop was rapidly taken up by zebrafish embryos, reaching a stable internal concentration between 48 and 72 hours.

5.1.3 Distribution

Yenne (1990), an unpublished study, examined the tissue distribution of radiolabeled ethoprop following oral gavage or intravenous (*i.v.*) administration to rats. Peak levels of radioactivity in blood were observed within 30–42 minutes (T_{max}) of a single oral gavage dose of ^{14}C-labeled ethoprop (4 or 12.5 mg/kg-bw in females; 4 or 25 mg/kg-bw in males). The level of radioactivity in blood gradually declined over the next 24 hours with an elimination half-life of 92 hours (for the 12.5 mg/kg group) to 135 hours (for the 25 mg/kg group).

Once 90% of the radioactive dose was excreted, or up to 168 hours following oral or *i.v*. dosing of the rats, tissues were collected and residual radioactivity measured. After a single *i.v.* dose, residual tissue levels of radioactivity were low (~2.7% of the administered dose) and were primarily located in the liver, kidneys, lungs, and abdominal fat. Similar patterns and results were observed after single or multiple oral doses of ethoprop.

5.1.4 Metabolism

One study in ethoprop-exposed humans analyzed urine samples from agricultural applicators for the ethoprop metabolite, O-ethyl S-propyl phosphorothioate, over the course of 4 days after initial exposure (Lunchick et al. 2005). Data from this study suggest metabolism is rapid since this urinary metabolite was detected in all of the first 12-hour urine samples. Data from the subset of workers exposed to ethoprop only on the study's first day suggest that metabolism is complete within the first 24 hours, as the metabolite was not detected in urine samples collected during the 24- to 72-hour intervals.

In vivo studies in rats and zebrafish and *in vitro* studies in rat and rabbit microsomes indicate that ethoprop is rapidly metabolized and primarily undergoes de-propylation (loss of one S-propyl group), with O-de-ethylation also occurring, probably via a glutathione-dependent pathway (Grasse et al. 2024; Iqbal and Menzer 1972; Yenne 1990). In rats, as noted above, metabolism of ethoprop was complete within six hours of oral administration (Iqbal and Menzer 1972). Detection of O-ethyl S-propyl phosphorothioate in human urine (Lunchick et al. 2005) demonstrates that de-propylation also occurs in humans. Due to ethoprop's single-bonded S-ester linkages with phosphorus, it does not behave like typical phosphorodithioate insecticides (Iqbal and Menzer 1972). A proposed metabolic scheme based on studies in rats and humans is presented in Figure 2.

The principal product of de-propylation is O-ethyl S-propyl phosphorothioate, the primary water-soluble metabolite detected in rat urine and in studies with rat liver

microsomes and supernatant *in vivo* and *in vitro* (Iqbal and Menzer 1972), in human urine (Lunchick et al. 2005), and in whole zebrafish embryos (Grasse et al. 2024). In Yenne (1990), the directly characterized de-propylation product was the structurally related O-ethyl S-propyl phosphorodithioate (referenced as U5 by study authors), which retains an SH group bound to the phosphate; O-ethyl S-propyl phosphorothioate was not identified in that study but was postulated as an upstream intermediate. Iqbal and Menzer (1972) identified two downstream products of O-ethyl S-propyl phosphorothioate — ethyl phosphate and S-propyl phosphorothiolic acid —in rat urine and in studies with rat and rabbit liver microsomes. Ethyl phosphate was proposed to result from hydrolysis of O-ethyl S-propyl phosphorothioate at the remaining S-propyl ester bond, and S-propyl phosphorothiolic acid from hydrolytic loss of the ethoxy group (Iqbal and Menzer 1972). Ethyl phosphate was also identified by Yenne (1990) in rats and Grasse et al. (2024) in zebrafish, making it the metabolite most consistently identified across all three animal studies. Traces of methyl propyl sulfide, methyl propyl sulfoxide, and methyl propyl sulfone were additionally identified in rat urine from the propyl-radiolabeled compound only, proposed to result from S-methylation and sequential oxidation of the propyl thiolate ion released from ethoprop (Iqbal and Menzer 1972).

A second metabolic route involves glutathione-dependent O-de-ethylation, in which glutathione acts as an ethyl acceptor to produce S,S-dipropyl phosphorodithioic acid and S-ethylglutathione (Iqbal and Menzer 1972). S,S-Dipropyl phosphorodithioic acid was detected as a minor metabolite in rat urine and in rat and rabbit liver supernatant; the authors noted its instability and proposed its conversion to S-propyl phosphorothiolic acid (Iqbal and Menzer 1972). S-Ethylglutathione was detected only *in vitro* in rat liver supernatant incubated with reduced glutathione and was not found in rat urine (Iqbal and Menzer 1972). In zebrafish embryos, Grasse et al. (2024) additionally identified O-ethyl O-methyl S-propyl phosphorothioate and a conjugate of O-ethyl S-propyl phosphorothioate, along with the principal metabolites O-ethyl S-propyl phosphorothioate and ethyl phosphate. In Yenne (1990), three partially characterized urinary metabolites (referred to as U2–U4), speculated to be conjugates of ethyl phosphate and O-ethyl S-propyl phosphorothioate, together accounted for the majority of urinary radioactivity, suggesting that conjugation is a significant but incompletely characterized pathway. Overall, the major metabolites of ethoprop are shared across rats and zebrafish, and detection of O-ethyl S-propyl phosphorothioate in human urine suggests similar metabolism occurs in humans.

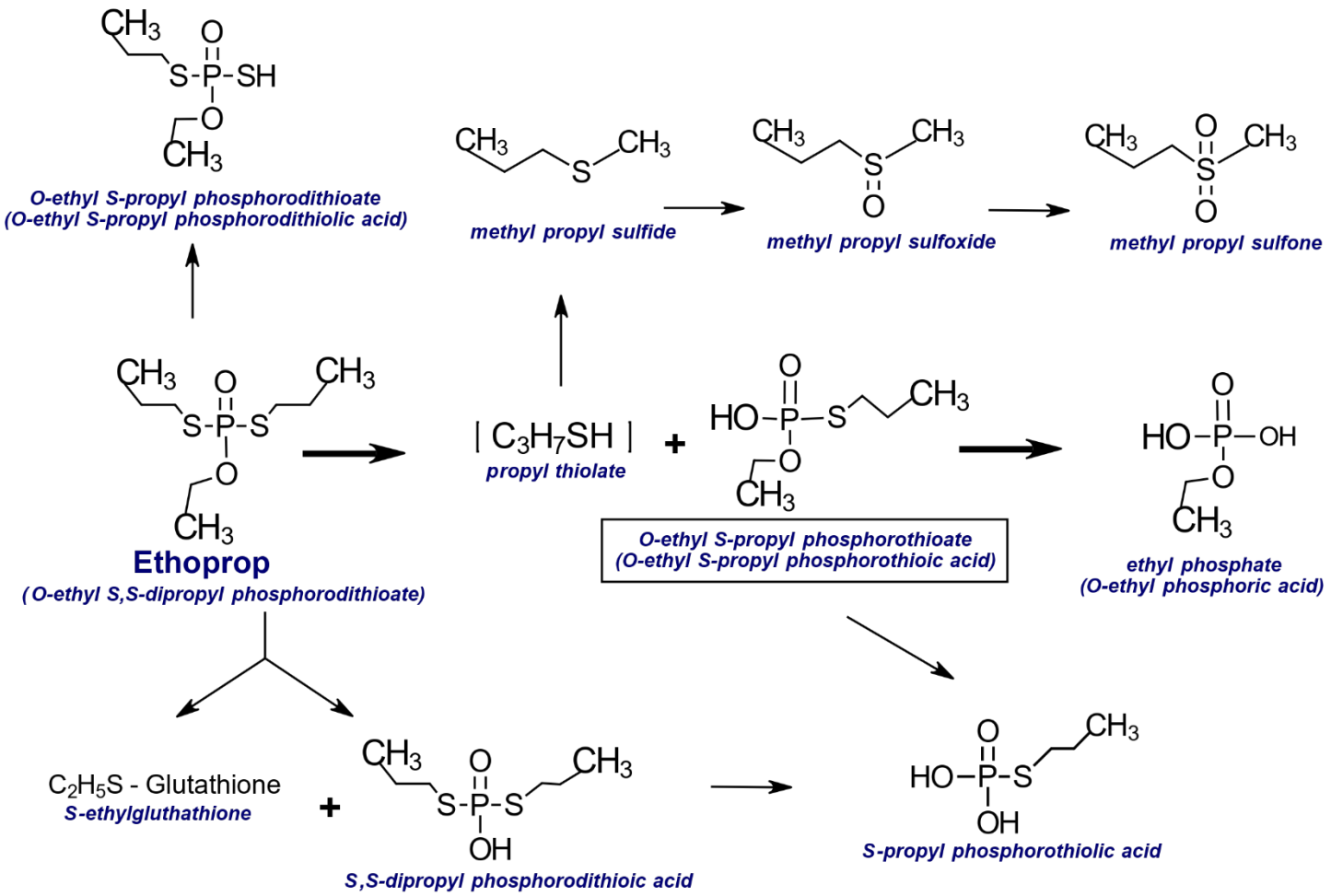


Figure 2. Proposed metabolic scheme based on studies in humans (Lunchick et al. 2005) and rats (Iqbal and Menzer 1972; Yenne 1990 [unpublished study]).

Brackets indicate production of an intermediate product; boxed metabolite has been detected in humans; bolded arrows indicate a primary pathway and product.

5.1.5 Elimination

Urinary excretion of the ethoprop metabolite O-ethyl S-propyl phosphorothioate was reported in the study of agricultural applicators by Lunchick et al. (2005). In this study, among workers exposed only on the first of four days, urinary excretion of this metabolite was complete within 24 hours.

Studies in rats indicate that ethoprop is rapidly eliminated as urinary and fecal metabolites (Iqbal and Menzer 1972; Yenne 1990) and in expired air (Yenne 1990). Male and female rats given single oral doses of O-ethyl-^{14}C or S-propyl-^{14}C labeled ethoprop excreted 50–65% of the labeled dose in urine, with less than 1% detected in feces; most radioactivity was eliminated within 6 hours of treatment (Iqbal and Menzer 1972). Because the side-chain-^{14}C-labels used in this study are susceptible to dealkylation, the recovery data could underestimate the overall elimination process.

Similarly, in rats administered ^{14}C-labeled ethoprop by the oral route under various dosing regimens (a single *i.v.* dose of 4 mg/kg or single oral dose of 4, 12.5, or 25 mg/kg or oral administration of 4 mg/kg/day non-labeled ethoprop for 14 days followed by a ^{14}C-labeled dose on day 15), excretion of radioactivity occurred predominantly via urine (50–59% of the administered dose), with most urinary excretion occurring within 24 hours post-administration (Yenne 1990). Fecal (7–16%) excretion and excretion in respired air (11–19%) were secondary routes. Excretion of radioactivity appeared to be independent of sex, dose route, dose level, and dose frequency (Yenne 1990).

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 15). KCs are characteristics of agents that cause cancer. This is 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 often is incomplete. The KC approach has emerged as a useful construct in literature assessments for organizing mechanistic evidence because KCs 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 15. 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; CAs chromosomal aberrations; ER, estrogen receptor; MN, micronuclei; 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 of carcinogens to systematically identify, organize, and summarize mechanistic information from studies conducted with ethoprop. Data for four of the ten KCs were identified, namely KC2, KC5, KC6, and KC8, and are summarized in the following sections.

5.2.1 KC2. Is genotoxic

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 substitutions, frameshifts, and small deletions or insertions, and chromosomal effects such as chromosomal aberrations (CAs), micronuclei (MN), and aneuploidy. Examples of DNA damage include DNA adducts, DNA strand breaks, and oxidative damage to DNA, such as 8-hydroxydeoxyguanosine (8-OHdG).

Several genotoxicity studies conducted by the pesticide registrant are summarized by CDPR (1995) and US EPA (1997a). OEHHA identified additional genotoxicity studies through literature review. Chromosomal effects and DNA damage were assessed in ethoprop-exposed mice and fish *in vivo* and in animal cells *in vitro*. The mutagenicity of ethoprop has been investigated in studies conducted in rats *in vivo*, animal cells *in vitro*, and bacterial and plant systems.

The findings from these studies are summarized below.

Genotoxicity studies of ethoprop in laboratory animals

Chromosomal Effects

- Chromosomal aberrations (CAs) were statistically significantly increased in bone marrow cells of male Swiss albino mice (n=3/group) exposed to 0.16 mg/kg-bw ethoprop (90% purity) for 14 days via oral gavage. No significant differences in CAs were observed in mice (n=3/group) that received a single dose of 0.16 mg/kg-bw ethoprop compared to controls (El-Gendy et al. 2019).
- Statistically significant time-dependent increases in CAs were observed in bone marrow cells of male Swiss albino mice (n=6/group) exposed to 0.16 mg/kg-bw ethoprop (90% purity) via oral gavage for 7 and 28 days compared to controls (El-Gendy et al. 2023).
- No induction of CAs were observed in bone marrow cells from male SD rats administered 0, 2, 9, or 20 mg/kg ethoprop (95.7% purity) by oral gavage (dose group size and duration not reported). Severe toxicity was observed in the high-dose group. (Skinner and Schreiner 1981, as cited in CDPR 1995).
- Micronuclei frequency was statistically significantly increased in erythrocytes in Nile tilapia (*Oreochromis niloticus*) (n=30/group) exposed to 96 µg/L ethoprop (40% emulsifiable concentrate) for 7, 14, 21, or 28 days compared to controls (El-Gendy et al. 2025). Micronuclei frequency increased with exposure duration.

DNA damage

- DNA fragmentation was statistically significantly increased in brain tissue of male ICR (CD-1) mice (n=5–9) administered a single intraperitoneal injection of 200 µL/kg ethoprop (purity reported as analytical grade or highest grade available) compared to controls (Bagchi et al. 2001).
- The level of 8-OHdG was statistically significantly increased in livers from adult Nile tilapia fish (*Oreochromis niloticus*) (n=50) exposed to 0.096 mg/L ethoprop (40% emulsifiable concentrate) for 4 weeks compared to controls (El-Gendy et al. 2024).

Mutagenicity

- In a dominant lethal test in SD rats, pre-implantation loss and death of implants were observed at all dose levels of ethoprop. Ethoprop (purity not stated) was administered to male rats (n=10/group) at 0, 2, 9, and 20 mg/kg for 5 days via oral gavage (Putman 1981, as cited in CDPR 1995). At 20 mg/kg, severe toxicity was reported.
- No dominant lethal effect was observed in a study of male CD (SD) rats (n=24/group) administered 0, 1, 5, or 20 mg/kg ethoprop (95% purity) for 5 days via oral gavage (Dearlove 1987, as cited by CDPR 1995).

Genotoxicity studies of ethoprop in animal cells in vitro

Chromosomal Effects

- CAs were observed in Chinese hamster ovary (CHO) cells incubated with ethoprop (purity not stated) in the presence of S9 activation in two experiments, but not in the absence of S9 activation in a third experiment. In the first experiment, CHO cells were incubated for 5 hours with 0, 50, 150, or 300 µg/mL ethoprop followed by 14 to 18 hours of incubation without activation. No CAs were observed in cells exposed to ethoprop without S9 activation. In the second experiment, CHO cells were incubated with 0, 10, 30, or 60 µg/mL ethoprop for 5 hours followed by incubation with rat liver S9 fraction for 14 to 18 hours. CAs were induced at 60 µg/mL ethoprop with S9 activation. In the third experiment, CHO cells were incubated with 0, 50, 55, 60, 65, or 70 µg/mL ethoprop for 5 hours followed by incubation with S9 activation for 14 to 18 hours. CAs were induced at all concentrations of ethoprop in the third experiment (SanSebastian 1985, as cited in CDPR 1995).
- Sister chromatid exchanges (SCEs) were observed in CHO cells incubated with ethoprop (purity not stated) in the presence of S9 activation in two experiments, but not in the absence of S9 activation in a third experiment. In the first experiment, CHO cells were exposed to ethoprop between 0 to 350 µg/mL

without S9 activation for 5 hours. No increase in SCE was observed in cells without S9 activation. In the second experiment, CHO cells were exposed to ethoprop concentrations ranging from 0 to 60 µg/mL for 5 hours followed by incubation with rat liver S9 fraction for 29 hours, and in the third experiment, CHO cells were exposed to ethoprop concentrations ranging from 50 to 75 µg/mL for 5 hours followed by incubation with rat liver S9 fraction for 29 hours. Statistically significant and dose-dependent increases in SCE were observed in the second and third experiments (SanSebastian 1986, as cited in CDPR 1995).

DNA damage

- Statistically significantly increased DNA double strand breaks (as measured by the neutral comet assay) were observed in cultured *Cyprinus carpio* (carp) cells exhibiting fibroblast morphology exposed to 104.113 ppm ethoprop (purity ≥95%) for 6 hours (So et al. 2025).
- Unscheduled DNA synthesis was not observed in rat hepatocytes incubated with ethoprop (purity not stated). Cells were incubated with 2.5–100 µg/mL ethoprop in one study (duration not specified) (Myhr 1980, as cited in CDPR 1995), and 0.33–10,000 µg/well ethoprop for 18–20 hours in a second study (Barfknecht 1985b, as cited in CDPR 1995).

Mutagenicity

- No increase in mutations was observed in mouse lymphoma (L5178Y) cells exposed to ethoprop (technical grade) tested between 0.0316–0.237 µL/mL without activation or 0.0032–0.0316 µL/mL with rat liver S9 activation (Thompson and Blackburn 1981, as cited in CDPR 1995).
- No increase in forward mutations was observed in CHO (CHO-K1-BH4) cells exposed to 0–500 µg/mL ethoprop (purity not reported) for 5 hours without S9 activation or 0–150 µg/mL ethoprop with rat liver S9 activation (Stankowski 1985, as cited in CDPR 1995).

Genotoxicity studies in bacterial and plant systems

Mutagenicity

- Ethoprop (commercial grade, assumed to be between 85 to 90%) induced mutations at the *Waxy* locus in *Zea mays* (corn) *in situ* (Gentile et al. 1982).

- No mutagenic activity was reported for ethoprop (commercial grade, assumed to be between 85 to 90%) in reverse mutation tests conducted in multiple *S. typhimurium* strains[9] (Gentile et al. 1982).
- Other studies did not find increases in mutations in reverse mutation tests conducted in *S. typhimurium* strains[1] when exposed to 0–1000 µg/plate ethoprop (purity not specified) with or without S9 activation (Barfknecht 1985a, as cited in CDPR 1995) or when exposed to 0–5 µL/plate ethoprop (97.5% purity) with or without S9 activation (Brusick 1976, as cited in CDPR 1995).
- No mutagenic activity was reported in reverse mutation tests in *S. cerevisiae* strain D4 exposed to 0–5 µL/plate ethoprop (97.5% purity) with or without S9 activation (Brusick 1976, as cited in CDPR 1995). No cytotoxicity was reported at the tested concentrations.

Overall, chromosomal effects, DNA damage, and mutagenicity were observed in studies of ethoprop conducted *in vivo* and *in vitro*. Increases in CAs were observed in the bone marrow of male Swiss albino mice in two studies, but not in SD rats in one study. Increases in micronuclei and 8-OHdG levels were observed in fish and an increase in DNA fragmentation was observed in brain tissue of mice exposed *in vivo*. Dominant lethal mutations were observed in one study in SD rats, but not in another in CD (SD) rats. CAs and SCEs were increased in CHO cells exposed to ethoprop with S9 rat liver activation. DNA double strand breaks were increased in fish cells *in vitro*, but no evidence of unscheduled DNA synthesis was observed in rat hepatocytes exposed *in vitro*. Reverse mutations were increased in ethoprop-exposed corn, while no evidence of mutagenicity was observed in studies conducted in mouse lymphoma cells, CHO cells, *Salmonella typhimurium*, or *S. cerevisiae*.

5.2.2 KC5. Induces oxidative stress

Oxidative stress refers to an imbalance between the production and elimination of reactive oxygen and nitrogen species (ROS, RNS). Oxidative stress may contribute to the carcinogenic process by causing DNA mutations, chromosomal damage, genomic instability, and altered cell cycle regulation (Reuter et al. 2010).

Biomarkers for oxidative stress include 8-OHdG (indicative of oxidative damage to DNA that is linked to mutagenesis and carcinogenesis; also discussed in Section 5.2.1 KC2), ROS or RNS production, malondialdehyde (MDA) or 8-isoprostane (two common markers for lipid peroxidation), total antioxidant capacity, glutathione status [e.g.,

[9] Ethoprop was tested in the following bacterial strains (with and without metabolic activation): TA98, TA100, TA 1535, TA1537, and TA1538.

reduced glutathione (GSH), glutathione disulfide (GSSG), GSH/GSSG ratio; glutathione-S-transferase (GST), and glutathione reductase (GR), glutathione peroxidase (GPx)], and other antioxidant enzyme activities and expression levels [e.g., superoxide dismutase (SOD), catalase (CAT)].

OEHHA identified in the scientific literature studies that assessed the induction of oxidative stress following ethoprop exposure. These included ethoprop-exposed rats and fish *in vivo* and rats *in vitro*.

The findings from these studies are summarized below.

Oxidative stress in animal studies in vivo

- Statistically significant and dose-dependent increases in nitric oxide (NO, a reactive nitrogen species) and MDA (a biomarker of lipid peroxidation) levels were observed in brain tissue of male rats (n=8) exposed to 0, 0.56, 1.12, and 2.24 mg/kg/day ethoprop (95% technical grade) in corn oil by oral gavage for 90 days. These increases in brain NO and MDA levels were accompanied by statistically significant and dose-dependent decreases in brain GSH, SOD, and CAT activity levels (Ibrahim et al. 2021).
- Liver 8-OHdG levels were statistically significantly increased in adult Nile tilapia fish (n=50) exposed to 0.096 mg/L ethoprop (40% emulsifiable concentrate) at 1, 2, 3, and 4 weeks compared to controls (El-Gendy et al. 2024). Additionally, lipid peroxidation (LPO) levels and GST activity were statistically significantly increased, and SOD, CAT, and GPx activity and GSH levels were statistically significantly decreased in a time-dependent manner when measured weekly over the 4-week period.
- Significantly increased ROS was observed in a concentration-dependent manner in zebrafish embryos (n=3 wells/assay, 20 embryos/well) exposed to 0, 10, 20, or 30 mg/L ethoprop (analytical standard) from 6 hours post fertilization (hpf) to 72 hpf. MDA levels were significantly increased at all concentration levels. SOD activity decreased in a concentration-dependent manner with statistically significant decreases at 20 and 30 mg/L. CAT activity significantly increased at 20 mg/L (Li et al. 2021).
- No effect on liver LPO levels, GST activity, or CAT activity was observed in mature banded tetra fish (*Astyanax aeneus*) (> 4 cm body size) (n=15) exposed to 0.014 mg/L ethoprop (purity not reported) for 48 hours (Sandoval-Herrera et al. 2019).
- No significant differences in LPO levels or GST activity were observed in gar (*Astractosteu tropicus*, a type of fish) larvae (5 days old) (n=10) exposed to concentrations of ethoprop (purity 98%, based on personal communication with authors) between 500 to 1500 µg/L for 96 hours (Mena Torres et al. 2012).

Oxidative stress in rodent studies in vitro

- Lipid peroxidation, as measured by MDA production, was induced in hepatocytes isolated from adult male SD rats incubated for 90 minutes with ethoprop (99% purity) at 1 mM but not at 10 or 100 µM (Yamano and Morita 1995).

Overall, evidence for ethoprop-induced oxidative stress was generally consistent both across the multiple biomarkers measured within individual studies, and across studies that assessed specific biomarkers, such as oxidative damage to DNA (one study), production of reactive oxygen or nitrogen species (two studies), markers of LPO (four studies reported increases; two reported no changes), decreased GSH (one study), and changes in antioxidant enzyme activity (three studies; two additional studies reported no changes). In the one study that assessed oxidative damage to DNA, increased liver 8-OHdG and LPO levels were observed in Nile tilapia, along with changes in antioxidant enzyme activity. In the two studies that assessed production of reactive oxygen or nitrogen species, increased reactive nitrogen species (nitric oxide) and MDA levels, decreases in GSH, and changes in antioxidant enzyme activity were observed in brain tissues of ethoprop-exposed male rats, and increased ROS and MDA levels and changes in antioxidant enzyme activity were observed in zebrafish embryos. The fourth study to observe an increase in MDA levels was conducted in rat hepatocytes, while the two other studies assessing LPO, conducted in fish (adult tetras and gar larvae), reported no changes in either LPO or antioxidant enzyme activity.

5.2.3 KC6. Induces chronic inflammation

Chronic inflammation can trigger cellular events associated with carcinogenesis, such as cellular transformation, promotion and survival of transformed cells, proliferation, invasion, angiogenesis, and metastasis (Aggarwal et al. 2006; Sethi et al. 2008; Smith et al. 2020). Several pro-inflammatory molecules have been identified, including the cytokines tumor necrosis factor-alpha (TNF-α), transforming growth factor-β (TGF-β) and several interleukins (ILs) such as IL-1α, IL-1β, IL-6, IL-8, IL-18, chemokines, and others (Aggarwal et al. 2006; Landskron et al. 2014). During chronic inflammation, cytokines can induce cell transformation and malignancy, conditional on the balance of pro- and anti-inflammatory cytokines, their relative concentrations, cytokine receptor expression levels, and the activation state of surrounding cells (Landskron et al. 2014).

OEHHA identified in the scientific literature one study of ethoprop with endpoints related to chronic inflammation; however, it is not a chronic study. This study is summarized below.

- In zebrafish embryos (n=3 wells/assay, 20 embryos/well) exposed to 0, 10, 20, or 30 mg/L ethoprop (analytical standard) from 6 hpf to 72 hpf, a concentration-

dependent and statistically significant increase in gene expression of *Tnfα* was observed for the 20 and 30 mg/L ethoprop-exposed groups. *IL1β* gene expression was also statistically significantly increased in the 20 mg/L and 30 mg/L groups (Li et al. 2021).

5.2.4 KC8. Modulates receptor-mediated effects

Chemicals may modulate receptor-mediated effects in a variety of ways, including binding to and either activating or inactivating a receptor, altering receptor levels or function, altering levels of endogenous ligands that are available to bind to the receptor, or otherwise altering receptor-mediated gene expression or intracellular signaling. Many cellular receptors regulate critical cellular pathways, such as those involved in differentiation and proliferation, the disruption of which can contribute to carcinogenic processes. For example, activation of certain growth factor receptors, or estrogen, androgen, or progesterone receptors can lead to the development of various types of cancer in humans and animals. As another example, activation of the aryl hydrocarbon receptor is involved in the development of a number of different types of cancers in humans and animals. Activation of other nuclear receptors, including peroxisome proliferator activated receptor alpha (PPARα) and the constitutive androstane receptor (CAR), also has been associated with carcinogenesis (Smith et al. 2020).

The only data OEHHA identified for ethoprop relevant to KC8 were from testing performed as part of the US EPA's Endocrine Disruptor Screening Program (EDSP) Tier I screening battery (US EPA 2015a, b). The EDSP Tier I screening battery consists of 11 assays:

- amphibian metamorphosis assay (frog)
- androgen receptor binding assay (rat prostate cytosol)
- aromatase (CYP19) inhibition assay (microsomes expressing human recombinant CYP19)
- estrogen receptor binding assay (rat uterine cytosol)
- estrogen receptor transcriptional activation assay (human cell line hERα-HeLa-9903)
- fish short-term reproduction assay (fathead minnows)
- steroidogenesis assay (human adrenocortical cell line H295R)
- female pubertal assay (rat)
- male pubertal assay (rat)
- Hershberger assay (male rat)
- uterotrophic assay (female rat)

Use of this EDSP Tier I screening battery is intended to identify chemicals that may have potential interactions with the estrogen, androgen, and thyroid pathways, and to determine if additional testing (i.e., Tier II testing) is warranted (https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-tier-1-assessments). Findings from the EDSP Tier I screening battery relevant to KC8 are summarized below.

- The amphibian metamorphosis assay was conducted in African clawed frog (*Xenopus laevis*) larvae at Nieuwkoop-Faber (NF) stage 51 (n=80 [total, across four replicates] per group, with 20 larvae per replicate). This assay is intended to screen for effects on the hypothalamus-pituitary-thyroid (HPT) axis. Larvae were exposed to 0, 0.01, 0.10, or 1.0 mg/L of ethoprop. At days 7 and 21, ethoprop significantly decreased hind-limb length (HLL) by 16.6 and 18.0%, respectively in the 1 mg/L group. At day 7, snout-vent length (SVL) was reduced by 9.5 and 13.7% in the 0.013 mg/L and 0.95 mg/L groups, respectively. No treatment-related effects were reported on thyroid histopathology. This assay was considered negative for effects on the HPT axis, based on the lack of treatment-related histopathology changes in the thyroid.
- Ethoprop tested negative ("non-binder") in the *in vitro* androgen receptor (AR) binding assay. This is a competitive binding assay using ventral prostate cytosol from male SD rats as the AR source. Ethoprop was tested at concentrations ranging from 0.00001 to 1000 µM and did not inhibit binding of the radiolabeled ligand ([^{3}H]-R1881) to the AR at any concentration.
- The ability of ethoprop to inhibit aromatase (CYP 19) activity was evaluated *in vitro* using human recombinant aromatase and tritiated androstenedione as the substrate. Some inhibition (40%) was reported at the highest ethoprop concentration tested (1000 µM), with a high degree of variation in the slope of the concentration response curve at lower concentrations (26.6% coefficient of variation). These results were considered equivocal by the testing laboratory.
- Ethoprop tested negative ("not interactive") in the *in vitro* estrogen receptor (ER) binding assay. This is a competitive binding assay using uterine cytosol from female SD rats as the ER source. Ethoprop was tested at concentrations ranging from 0.0001 to 1,000 µM and did not inhibit binding of the radiolabeled ligand ([^{3}H]-17β-estradiol) to the ER.
- Ethoprop tested negative in the estrogen receptor alpha (ERα) transcriptional activation assay in hERα-HeLa-9903 cells (human cervical cancer cell line). Ethoprop was non-cytotoxic in this assay at all concentrations tested (0.00005–5 µg/mL).
- The fish short-term reproduction assay is a 21-day study conducted in male and female fathead minnows (*Pimephales promelas*). Five-month-old, adult fish (24

fish per group; two males and four females) were exposed to ethoprop (96.6% purity) at 0.004, 0.02, and 0.1 mg/L. There was no observed effect on survival. Mean fecundity (eggs/female/day/replicate) was 38% lower in the 0.1 mg/L group (with cessation of fecundity in one replicate) compared to control, although the decrease did not reach statistical significance. Fertility was 4.5% lower in the 0.1 mg/L group compared to control ($p = 0.01$). Post-ovulatory follicle scores were significantly decreased in the 0.1 mg/L group compared to control, consistent with fewer females in this group found to be at the time of, or immediately after, ovulation. In males treated at 0.02 and 0.1 mg/L, the median nuptial tubercle scores (expression of nuptial tubercles is a secondary sexual characteristic) were significantly decreased compared to control. There were no significant effects on GSI (gonado-somatic index) or plasma VTG (vitellogenin) in either sex, or on female median tubercle scores.

- A steroidogenesis assay was performed in three sets of experiments using a human adrenocortical cell line, H295R. Two experiments tested ethoprop (96.6% purity) at 0, 0.0001, 0.001, 0.01. 0.1, 1, 10, and 100 µM, while the third experiment tested ethoprop at 0, 0.1, 1, 5, 10, 20, 50, and 100 µM for 48 hours. No treatment-related cytotoxicity was observed in any experiment. A dose-related increase in estradiol concentration was observed for ethoprop at concentrations ≥10 µM in all three experiments, and at concentrations ≥5 µM in the third experiment. The effect of ethoprop on testosterone synthesis was judged to be equivocal, with a statistically significant decrease observed at 100 µM in one experiment, no effects observed in a second experiment, and non-dose-related decreases in the third experiment at all doses tested.
- In the female rat pubertal assay, SD rats (n=15 per dose group) were treated daily via oral gavage (5 mL/kg) with 0, 3, or 6 mg/kg/day ethoprop (96.6%) in corn oil from postnatal day (PND) 22 to 42. No treatment-related effects were reported on the timing of vaginal opening (VO), or on serum levels of thyroxine (T4) or thyroid stimulating hormone (TSH).
- In the male rat pubertal assay, SD rats (n=15 per dose group) were treated daily via oral gavage (5 mL/kg) with 0, 3, or 6 mg/kg/day ethoprop (96.6%) in corn oil from PND 23 to 53. Serum testosterone levels decreased dose-dependently ($p < 0.001$) by 33% and 51% at 3 and 6 mg/kg/day, respectively. Serum thyroxine (T_4) levels increased by 28% ($p < 0.001$) with a corresponding non-significant decrease of 16% in serum TSH levels in the 6 mg/kg/day group. Significant reductions ($p < 0.05$) in pituitary weight (10%) and epididymis weight (11%) (effect seen only on the right, but not the left epididymis) and significant increases in thyroid weight (17%) were observed in the 6 mg/kg/day group. No treatment-related effects were reported on the timing of preputial separation. The

6 mg/kg/day dose caused statistically significant inhibition of RBC (94%) and brain (34%) cholinesterase activity and in the 3 mg/kg/day group of 70% RBC and 25% in brain.

- The *in vivo* Hershberger assay is designed to assess androgenic and anti-androgenic effects in castrated male SD rats.
    - When ethoprop (0, 8, or 16 mg/kg/day ethoprop [96.6% purity] dissolved in corn oil via oral gavage for 10 days, starting on PND 54) was tested for androgenic activity a statistically significant increase in the weight of the ventral prostate was observed at 16 mg/kg/day. No other increases in weights of androgen sensitive tissues were observed, thus ethoprop was considered as testing negative for androgenic effects in this assay. Treatment at 8 and 16 mg/kg/day resulted in a statistically significant acetylcholinesterase (AChE) inhibition in red blood cells (83–88%) and (31–67%) in brain tissue in these studies.
    - When ethoprop (0, 1, 8, or 16 mg/kg/day ethoprop [96.6% purity] dissolved in corn oil via oral gavage for 10 days, starting on PND 54) was tested for anti-androgenic activity (i.e., under conditions where testosterone propionate in corn oil was co-administered at 0.4 mg/kg/day via subcutaneous injection) statistically significant decreases in the weight of the seminal vesicles, ventral prostate, and levator ani-bulbocavernosus muscle (LABC) were observed at 16 mg/kg/day. Ethoprop tested positive in this assay, since decreases in organ weight were observed in two or more androgen-sensitive tissues. AChE levels in red blood cells were significantly reduced at 1, 8, and 16 mg/kg/day (range of 35–76%). In brain, significant reductions in AChE levels were observed at 8 and 16 mg/kg/day (36 and 66%, respectively) compared to controls.
- The *in vivo* uterotrophic assay is designed to assess estrogenic effects in ovariectomized female SD rats. Ethoprop (96.6% purity) was administered at doses of 0, 2, 9, or 18 mg/kg/day in corn oil via oral gavage for 4 days to ovariectomized female SD rats (n=8 per group). Animals were sacrificed 24 hours after the last dose and uterine weights were recorded. Ethoprop tested negative in this assay, as no treatment-related effects on uterine weight were reported.

Overall, in this screening battery, ethoprop altered receptor-mediated effects in some of these assays, but not all. Namely, ethoprop exhibited anti-androgenic activity via decreased organ weights (seminal vesicles, ventral prostate, and LABC) in the *in vivo* Hershberger assay in male rats, decreased serum testosterone and epididymis weights in the *in vivo* pubertal assay in male rats, and reduced the median nuptial tubercle score (secondary sexual characteristic) in male fathead minnows. Ethoprop exhibited activity

suggestive of effects on the HPT axis in pubertal male rats via decreased pituitary weight, increased thyroid weight, increased serum thyroxine levels, and a non-significant decrease in serum TSH. Other effects of ethoprop included increased estrogen synthesis *in vitro* in a human adrenal cell line and decreases in fecundity (NS), fertility, and the number of post-ovulatory follicles in female fathead minnows. Ethoprop tested negative or the findings were equivocal for other outcomes assessed.

OEHHA notes that US EPA, in its EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays (US EPA 2015b) stated, “There is no convincing evidence for potential interaction with the estrogen or androgen-pathway for mammals and wildlife. There is insufficient complementarity of evidence within and redundancy across the assays for these pathways, particularly at the higher levels of the Tier 1 screening with dose levels that caused significant cholinesterase inhibition. Ethoprop appears to interact with the thyroid pathway only in mammals and the interaction is seen only at doses that caused severe cholinesterase inhibition.”

Of the three assays in which altered receptor-mediated effects were observed (the male rat pubertal assay, the male rat Hershberger and the short-term reproduction assay in fathead minnows) cholinesterase inhibition was reported in the male rat pubertal and in the Hershberger assays. However, in the Hershberg assay, there were no clinical signs of toxicity reported, and in the pubertal male rat study, no treatment-related clinical signs or effects on body weight were observed. In addition, there was no effect on survival at the doses tested in either of the rat studies or the fish study. Further, in two-year cancer bioassays conducted in male rats, no significant differences in survival were observed at doses up to 4.19 mg/kg/day in one study and up to 4.74 mg/kg/day in a second. In a third study, no effects on survival were observed in male rats exposed to 18.38 mg/kg/day until study week 84.

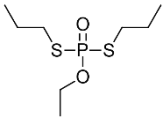
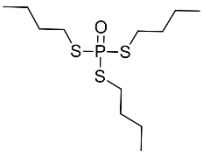
5.3 Structure Activity Considerations

When considering structure activity, the US EPA (1997a) identified four organophosphate compounds, all acetyl cholinesterase inhibitors, to compare to ethoprop: ebufos, disulfoton, terbufos and tribufos. This selection was based on a review on the structure-activity relationships of organophosphates by Woo et al. (1996). The Woo review noted that "organophosphorus compounds represent one of the most difficult structural classes of chemicals for predicting or assessing carcinogenic potential because of the complex interplay of multiple physicochemical and biological factors" (Woo et al. 1996).

Of the four compounds US EPA (1997a) identified for comparison with ethoprop, only tribufos (S,S,S-tributyl phosphorotrithioate) has been found to increase tumors in

carcinogenicity studies in rodents. Specifically, tribufos increased the incidence of rare adenocarcinomas of the small intestine in male and female mice, liver hemangiosarcomas in male mice, and lung alveolar/bronchiolar adenomas in female mice. Tribufos (S,S,S-tributyl phosphorotrithioate) is classified as a carcinogen ("likely to be carcinogenic to humans") by US EPA (US EPA 1997b) and has been listed under Proposition 65 for cancer since February 25, 2011 (https://oehha.ca.gov/proposition-65/proposition-65-list). Table 16 below compares the target tumor sites observed in animal studies of tribufos and ethoprop.

Table 16. Comparison of target tumor sites in in rats and mice for ethoprop and the structurally related chemical tribufos

Chemical [Cancer classification]	Structure	Tumor Sites in Mice	Tumor Sites in Rats
Ethoprop [P65: currently under consideration][1]		Liver • Hepatocellular carcinoma (F)	Adrenal gland • Malignant pheochromocytoma (M) Thyroid gland • C-cell adenoma, carcinoma, and adenoma and carcinoma (combined) (M) • Follicular cell adenoma (M) Uterus • Endometrial adenoma and adenocarcinoma (rare) (F) • Endometrial polyp, endometrial stromal polyp, and endometrial and stromal polyp (combined) (F) Liver • Hepatocellular adenoma, and adenoma and carcinoma (combined) (M)
Tribufos [P65, US EPA][2]		Liver • Hemangiosarcoma (M) Lung • Alveolar/bronchiolar adenoma (F) Small intestine • Adenocarcinoma (rare) (M, F)	No tumors observed in studies in M or F Fischer 344 rats

P65, Proposition 65 carcinogen; US EPA, United States Environmental Protection Agency; M, male; F, female.
[1]Tumor findings for ethoprop as reported in Section 4.
[2]Tumor findings for tribufos as reported in US EPA (1997b).

OEHHA also explored the use of Generalized Read-Across (GenRA)[10], which is a tool available on the US EPA website, to identify additional chemicals structurally similar to ethoprop. Of the candidate chemicals identified by this tool, all had similarity scores less than or equal to 0.32, where a score of 1 indicates identical similarity.

[10] https://www.epa.gov/comptox-tools/generalized-read-across-genra

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APPENDIX A: LITERATURE SEARCH ON THE CARCINOGENICITY OF ETHOPROP

Literature searches on the carcinogenicity of ethoprop were initiated in October 2025 and last updated in August 2026. 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. In addition, because ethoprop is a pesticide, toxicity data submitted by pesticide registrants to the California Department of Pesticide Regulation (CDPR) and US Environmental Protection Agency (EPA) were requested and reviewed.

When searching the published scientific literature, OEHHA used an approach similar to that recommended by the National Toxicology Program (NTP) Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2025; https://ntp.niehs.nih.gov/sites/default/files/2025-05/handbook_roc_508.pdf).

The searches were conducted by OEHHA scientists using the following approaches:

- Primary searches in major biomedical databases.
- Searches in other data sources, including authoritative bodies reviews and reports, and databases or web resources.
- Requests to CDPR and US EPA for toxicity data submitted by pesticide registrants.
- Additional focused searches on specific topics

Primary Search Process

Data Sources

Table A1 lists the data sources that were searched to find information on ethoprop. The list is adapted from the recommendations by the NTP RoC (NTP 2015), based on availability and suitability for this topic.

Table A1. Biomedical literature and other databases used in primary literature search

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

Search Term Identification

- The US EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) was used to identify synonyms for ethoprop.
- 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 NTP (2025) 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, SciFinder-n, Google Scholar, and ToxPlanet in October 2025 using the chemical name and synonyms. There were no limits on language, date, species or end points. Four separate searches were done in PubMed and Embase. 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

The basic structure used for each search is shown in Table A2 through Table A5. Detailed PubMed search strategies showing specific search terms and syntax are shown in Table A11 through Table A14.

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

Search step	Search Concepts
#1	Ethoprop 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 and Embase)

Search step	Search Concepts
#1	Ethoprop terms
#2	Cancer terms (PubMed Cancer Filter)
#3	Experimental Animals terms (RoC Strategy)
#4	#1 AND #2 AND #3

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

Search step	Search Concepts
#1	Ethoprop terms
#2	ADME terms (RoC Strategy)
#3	#1 AND #2

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

Search step	Search Concepts
#1	Ethoprop 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)

The searches were run first in PubMed. Then, the search terms were tailored according to the search features unique to other databases (i.e., Embase, SciFinder-n, Google Scholar, and ToxPlanet). 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 Table A6 and Table A7.

Table A6. Human cancer epidemiologic studies search structure (SciFinder-n)

Search step	Search Concepts
#1	Ethoprop 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 A7. Animal studies search structure (SciFinder-n)

Search step	Search Concepts
#1	Ethoprop terms
#2	Limit to journal article
#3	Limit to animal concept
#4	Limit to database “CAplus”
#5	EXCLUDE database Medline

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

Results from all databases were uploaded to EndNote and duplicates were removed. The total retrieval of the primary searches for ethoprop is shown in Table A8.

Table A8. Ethoprop primary search results

Search \ Database	PubMed Results	Embase Results	SciFinder-n Results	ToxPlanet Results	Google Scholar Results
Human cancer studies	3	20	7	0	4
Animal cancer studies	3	2	2	0	0
Pharmacokinetics and metabolism (ADME)	21	63	0	0	0
Studies on key characteristics of carcinogens and other mechanistic concepts	52	100	0	0	0
Total results before deduplication	79	185	9	0	4

Search Process for Other Online Data Sources

In addition to the primary searches listed above, focused searches were conducted by OEHHA scientists on the following topics: use and exposure, animal tumor pathology, spontaneous tumor incidence in historical controls, and relevant information on

structurally related chemicals. The most recent cancer classification by the European Union was identified by searching the European Chemicals Agency (ECHA) website.

Search Process for Pesticide Registrant Studies

Pesticide registrant studies on ethoprop were identified in documents and reports from US EPA and CDPR. Such studies are typically inaccessible to the public. Therefore, OEHHA submitted requests to US EPA or CDPR for these studies, which were then provided to OEHHA on a basis of confidentiality. OEHHA reviewed and cited the following studies in this document:

Studies obtained from US EPA:

- Ceuppens and Peers 2017
- Hardisty 2017a
- Hardisty 2017b

Studies obtained from CDPR:

- Barnett et al. 1983
- Davidson and Voss 1983
- Inoue 1984
- Spicer 1985
- Stoughton 1986
- Williams 1992
- Yenne 1990

Process for Additional Focused Literature Searches

Introduction (Section 1)

Studies for the Introduction (use, exposure, and review by other agencies) were mainly identified by the primary search. Chemical properties were extracted from US EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard). Additional focused searches on CDPR and US EPA websites were conducted to identify information on the registration and use of pesticides and on monitoring data of pesticide residues. OEHHA searched for additional monitoring data on ethoprop in the environment and ethoprop residue data on the US Department of Agriculture (USDA) website.

Animal tumor pathology observed in animal carcinogenicity studies (Section 4)

Focused searches on tumor pathology of rodents were conducted using:

- Suttie AW, Leininger JR, Bradley AE. 2018. Boorman's Pathology of the Rat (second edition). Academic press.
- Charles River Laboratories at www.criver.com.
- PubMed.

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

Structure-activity considerations (Section 5.3)

Focused searches on animal carcinogenicity studies of chemicals structurally related to ethoprop were conducted using US EPA's CompTox Chemicals Dashboard v2.8.0 (https://comptox.epa.gov/dashboard).

Literature Screening Processes

Development of PECO criteria and screening for supplemental materials

In order to guide the literature screening process, populations, exposures, comparators and outcomes (PECO) criteria were developed, along with descriptions of supplemental materials (Table A9 and Table A10). These criteria and supplemental material descriptions were used by OEHHA scientists to screen the primary literature search results.

Table A9. Populations, exposures, comparators, and outcomes (PECO) Criteria

Population	**Human:** Studies of any population and life stage (occupational or general population, including children and sensitive populations). **Nonhuman:** Nonhuman animal species (whole organism, including transgenic animals) of any life stage (including fetal, early postnatal, adolescents, and adults).
Exposure	**Chemical and commercial names and CAS number:** ethoprop, O-ethyl S,S-dipropyl phosphorodithioate, O-ethyl S,S-dipropyl ester phosphorodithioic acid, ethoprophos, and CAS number: 13194-48-4 **Human:** Exposure to ethoprop irrespective of exposure route. Exposure may be defined by measures of exposure for individuals (e.g., measurement in biospecimens, such as ethoprop metabolites measured in urine) or ecological studies using group or individual level data for exposure assessment. **Animal:** Exposure to ethoprop, irrespective of exposure route.
Comparators	**Human**: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of ethoprop. Case reports and case series will be considered as ”potentially relevant supplemental material.” **Animal**: A concurrent control group exposed to vehicle-only treatment, if a vehicle was used. Studies utilizing non-concurrent or historical control groups will be considered as “potentially relevant supplemental material.”
Outcomes	Benign and malignant neoplasms.

Table A10. Major categories of "potentially relevant supplemental material"

Category	Evidence
Mechanistic considerations and other data relevant to ethoprop carcinogenicity	*In vivo, in vitro, ex vivo*, and *in silico* studies reporting measurements related to carcinogenicity outcomes that inform the biological or chemical events associated with phenotypic effects, in both mammalian and nonmammalian model systems. Other studies with relevant molecular data and/or that inform mechanisms of action will also be included.
Pharmacokinetics and metabolism data (ADME)	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion. Studies describing metabolism in bacteria or model systems not applicable to humans or animals should not be tagged.
Production, use and exposure characteristics	Studies that inform understanding of the production and uses of ethoprop, exposure sources, environmental sampling, biomarkers of exposure, and measured concentrations in humans (e.g., biomonitoring data).
Mixture studies	Studies involving exposures to chemical mixtures containing ethoprop will be evaluated for informativeness on a case-by-case basis. This categorization generally does not apply to epidemiological studies where exposures are myriad, often uncontrolled, and exposure sources might be unclear.
Case reports or case series	Case reports describing carcinogenicity outcomes after exposure will be tracked as potentially relevant supplemental information.
Review or other records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Unnamed reports (other)	Other records identified that have no citation information (typically identified during gray literature searches).

Use of Health Assessment Workspace Collaborative (HAWC)

HAWC (https://hawcproject.org/about/) was used as a tool to screen and tag the results of the primary literature search. The literature was screened using the PECO criteria in Table A8 and descriptions of supplemental material in Table A9.

Importing the EndNote library into HAWC

Citations retrieved from the literature searches for ethoprop were uploaded to an EndNote library, and duplicates were removed. Next, the EndNote library was 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 two OEHHA scientists using PECO criteria and descriptions of supplemental materials based solely on titles and abstracts to eliminate studies or articles that do not meet the PECO criteria or contain information on any of the key topics identified as potentially relevant supplemental material. 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 the same PECO criteria and descriptions of supplemental materials as was used in the Level 1 screening. 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. Eligibility of any study that met PECO or supplemental material criteria was independently confirmed by another OEHHA scientist.

Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC. The tagging of a study to a key topic does not necessarily mean it was included in the final HID.

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

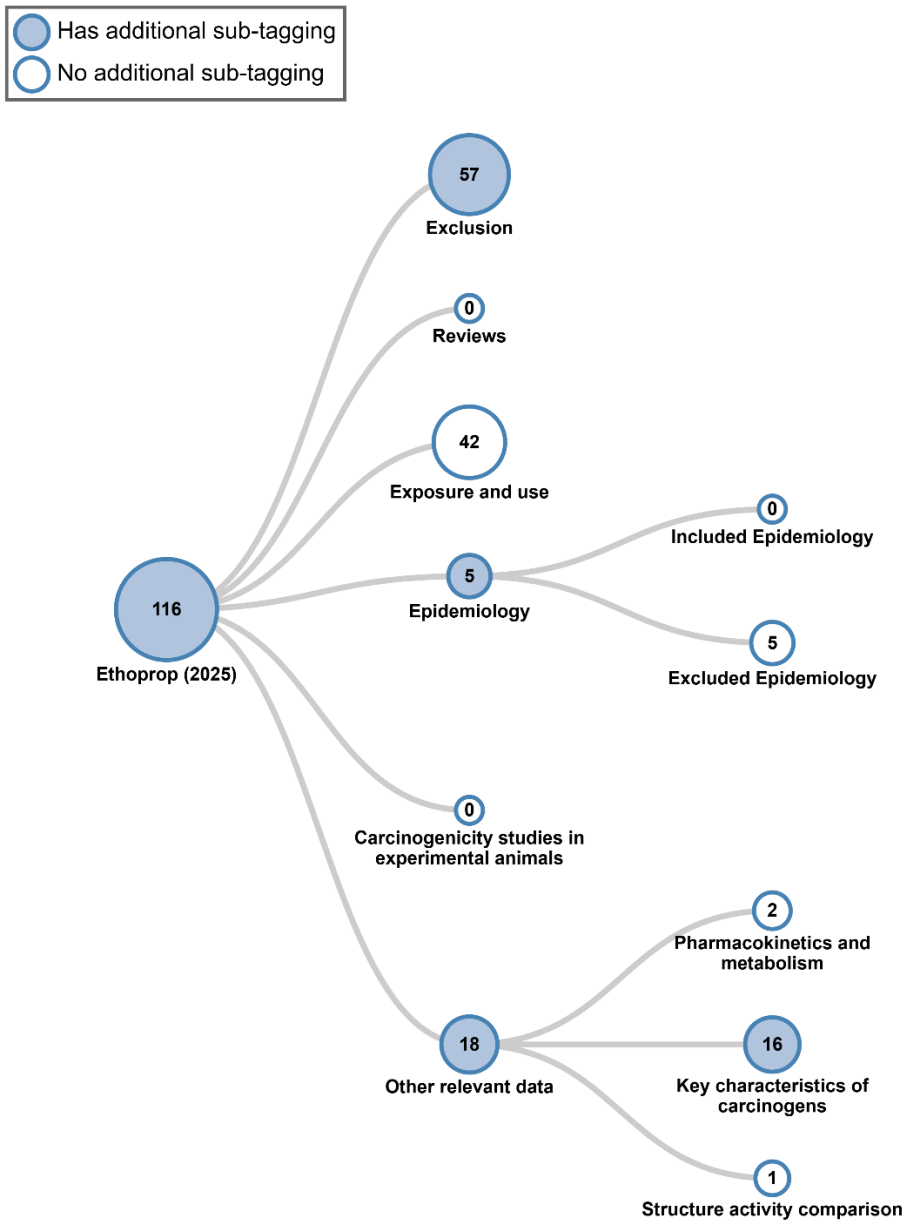

Figure A1. Overview of HAWC literature screening results for ethoprop.

The number of publications is indicated in each node of the literature tag tree.

Summary

More than 150 references, including peer-reviewed journal articles, government reports, and pesticide registrant studies, were identified for inclusion through these search strategies. Among these, over 80 references were cited in this document.

Detailed PubMed Literature Search Strategies – Primary Searches (Table A11 through Table A14)

Detailed PubMed search strategies showing specific search terms and syntax are shown in Table A11 through Table A14, below.

Table A11. PubMed Search Strategy for Human Cancer Studies

Set	Search Terms	Retrieval	Concept Group
1	"O-Ethyl S,S-dipropyl phosphorodithioate" OR "O-ethyl S,S-dipropyl ester phosphorodithioic acid" OR "Ethoprop" OR "Ethoprophos" OR "Ethoprofos" OR "13194-48-4"	199	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	8,166,075	PubMed Cancer terms

	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 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		

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	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	(("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 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])		RoC Human Epi terms
4	#1 AND #2 AND #3	2	Final

Table A12. PubMed Search Strategy for Animal Cancer Studies

Set	Search Terms	Retrieval	Concept Group
1	"O-Ethyl S,S-dipropyl phosphorodithioate" OR "O-ethyl S,S-dipropyl ester phosphorodithioic acid" OR "Ethoprop" OR "Ethoprophos" OR "Ethoprofos" OR "13194-48-4"	199	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	8,166,075	PubMed Cancer terms

	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 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] 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		

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	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 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	1,985,977	RoC Experimental Animals Terms

	((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	3	Combine Chemical + Cancer terms+ Animals terms

Table A13. PubMed Search Strategy for Pharmacokinetics and Metabolism (ADME) Studies

Set	Search Terms	Retrieval	Concept Group
1	"O-Ethyl S,S-dipropyl phosphorodithioate" OR "O-ethyl S,S-dipropyl ester phosphorodithioic acid" OR "Ethoprop" OR "Ethoprophos" OR "Ethoprofos" OR "13194-48-4"	199	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 ("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]))	3,393,038	RoC ADME
3	#1 AND #2	21	combine chemical with ADME

Table A14. PubMed Search Strategy for Key Characteristics of Carcinogens and Mechanistic Concepts

Set	Search Terms	Retrieval	Concept Group
1	"O-Ethyl S,S-dipropyl phosphorodithioate" OR "O-ethyl S,S-dipropyl ester phosphorodithioic acid" OR "Ethoprop" OR "Ethoprophos" OR "Ethoprofos" OR "13194-48-4"	199	chemical terms
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-	7,442,136	RoC Cancer KC

	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 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-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]))		
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	6,869,925	IARC Cancer KC

	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] 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 "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]))	3,602,959	RoC Other Mechanistic
5	#1 AND (#2 OR #3 OR #4)	52	Chemical + (KC or Other Mech)

APPENDIX B: 78-WEEK FEEDING STUDIES IN MALE AND FEMALE $B6C3F_1$ MICE (DAVIDSON AND VOSS 1983)

The Office of Environmental Health Hazard Assessment (OEHHA) is providing the following summary of the unpublished report by Davidson and Voss (1983) in this Appendix for completeness, as the report itself is not readily available. 78-week dietary studies in male and female $B6C3F_1$ mice were conducted at a contract lab facility, Food and Drug Research Laboratories, in New York from December 28, 1978, through July 3, 1980. Mice were obtained from Harland Industries, Indianapolis, Indiana. These studies had a number of serious limitations, including inadequate characterization of the technical grade substance tested, incomplete reporting, reporting errors, dosing errors (i.e., administration of 10X the intended dose, resulting in the death of 18 mice in the male study and nine mice in the female study), other survival issues (e.g., unusual losses in the male study by week 21 in both control and treated animals), and less-than-lifetime study duration. These studies are of limited informativeness due to these limitations and were not mentioned or discussed in the US Environmental Protection Agency (US EPA) 1997 or 2020 evaluations of ethoprop (US EPA 1997a; 2020).

Male and female $B6C3F_1$ mice were administered ethoprop (technical grade; percent active ingredient, i.e., ethoprop, not specified) in the diet at concentrations of 0, 15, 30, or 60 ppm starting at 4–6 weeks of age for 78 weeks. In these studies, each experimental group consisted of 60 males and 60 females, with interim sacrifices at 52 weeks of 10 animals per group, with the exception of controls in the male study, where 11 animals were sacrificed. Test diets were prepared by dissolving ethoprop in acetone and mixing with rodent chow; control diets consisted of rodent chow mixed with a comparable amount of acetone vehicle. Gross necropsy and histopathological examinations were conducted on all animals. The pathologist was aware of the treatment status of the animals/tissues during histopathological examination.

Male $B6C3F_1$ mice

OEHHA found errors in data reporting on survival and used individual animal data from the animal fate tables to calculate survival. In males, there were unusual losses of animals by week 21, with 12%, 8%, 5% and 8% of animals dying in the 0, 15, 30, and 60-ppm groups, respectively. Survival at termination was 80%, 90%, 84% and 48% in the 0, 15, 30, and 60 ppm groups, respectively. An increase in mortality occurred in the high dose group following a dosing error in week 54; animals in the 60-ppm group were inadvertently administered a dose ten-times higher (600 ppm) than the intended level, leading to 18 deaths during weeks 55 and 56. Mean body weights in the treated groups

were generally comparable to controls, with statistically significant differences in group mean body weights compared to controls occurring sporadically during the study.

No treatment-related tumors were observed in male mice following ethoprop administration for 78 weeks.

Non-neoplastic findings

A treatment-related increase in hyperplastic nodules of the liver was observed (0/59, 0/60, 1/60, and 5/58 at 0, 15, 30, and 60 ppm, respectively), with a statistically significant increase in the high dose group by pairwise comparison to controls ($p = 0.027$) and a statistically significant dose-related trend ($p = 0.0014$).

A non-significant increase in the incidence of liver foci of cellular alteration was observed, with incidences of 0/59, 0/60, 2/58, and 2/58 at 0, 15, 30, and 60 ppm, respectively (trend $p = 0.07$).

In male mice, dose-related inhibition of cholinesterase activity was observed in treated animals compared to controls. At week 52, plasma and red blood cell activities were reduced by 66 and 62%, respectively, in the low-dose group, by 71 and 69%, respectively, in the mid-dose group, and by 71 and 61%, respectively, in the high-dose group. At week 78, plasma and red blood cell cholinesterase activities were reduced by 37 and 69%, respectively, in the low-dose group, by 43 and 80%, respectively, in the mid-dose group, and by 50 and 80%, respectively, in the high-dose group.

Female $B6C3F_1$ mice

OEHHA found errors in data reporting on survival and used individual animal data from the animal fate tables to calculate survival. In females, unusual losses of animals occurred by week 13 and 21 with 8%, 13%, 12% and 15% of animals dying in the control, low, mid and high-dose groups, respectively, at week 13, and 15%, 22%, 20% and 22% of animals dying in the 0-, 15-, 30-, and 60-ppm groups, respectively, at week 21. At study termination, survival was reduced in females with 76%, 66%, 70%, and 54% survival in the 0-, 15-, 30- and 60-ppm groups, respectively. An increase in mortality occurred in the 60-ppm group following a dosing error in week 54; animals in the 60 ppm group were inadvertently administered a dose ten-times higher (600 ppm) than the intended level, leading to nine deaths during weeks 55 and 56. Mean body weights in the treated groups were generally comparable to controls, with statistically significant differences in all treated group mean body weights compared to controls occurring sporadically during the study.

No treatment-related tumors were observed in female mice following ethoprop administration for 78 weeks.

Non-neoplastic findings

A non-significant, treatment-related increase in the incidence of liver foci of cellular alteration was observed, with incidences of 0/59, 2/58, 2/60, and 3/59 across all livers examined at 0, 15, 30, and 60 ppm (trend p = 0.09).

In female mice, dose-related inhibition of cholinesterase activity was observed in treated animals compared to controls. At week 52, plasma and red blood cell activities were reduced by 58 and 70%, respectively, in the low-dose group, by 63 and 69%, respectively, in the mid-dose group, and by 72 and 84%, respectively, in the high-dose group. At week 78 (terminal sacrifice), plasma and red blood cell cholinesterase activities were reduced by 30 and 67%, respectively, in the low-dose group, by 36 and 64%, respectively, in the mid-dose group, and by 39 and 78%, respectively, in the high-dose group, compared to controls.

APPENDIX C: SUMMARY OF US EPA'S 1997, 1998, AND 2020 CLASSIFICATIONS OF THE CARCINOGENIC POTENTIAL OF ETHOPROP

Overview of assessments of adrenal pheochromocytoma and thyroid C-cell tumors in studies of ethoprop in SD rats (Williams 1992) and F344 rats (Spicer 1985)

In 1997, US Environmental Protection Agency (US EPA) evaluated the carcinogenic potential and classified ethoprop as a "likely" human carcinogen (US EPA 1997a). This classification was based on the following factors:

> "(i) presence of a rare and life-threatening (malignant) tumor (pheochromocytomas of the adrenal glands) in male Sprague-Dawley rats at the low dose in the absence of cholinesterase inhibition;
>
> (ii) occurrence of another type of tumor (C-cell carcinomas of the thyroid glands) in male rats in two strains (Sprague-Dawley and Fischer 344) in three different studies at doses that did cause cholinesterase inhibition; and
>
> (iii) evidence of clastogenicity in *in vitro* mutagenicity testing." (US EPA 1997a) (p. 25).

In 1998, after evaluating historical control data provided by the registrant, US EPA re-affirmed the classification of ethoprop as a "likely" human carcinogen (US EPA 2020, p. 6).

Following the US EPA's 1997 and 1998 cancer classifications, the registrant requested a carcinogenic re-assessment of ethoprop and proposed a reclassification of its cancer potential. The registrant submitted pathology re-evaluation reports by a pathology working group (PWG) organized by the registrant on adrenal pheochromocytomas and thyroid C-cell tumors in male rat studies by Williams (1992) and Spicer (1985) (Hardisty 2017a; 2017b). The registrant also submitted statistical analyses using Poly-K tests by the PWG (Ceuppens and Peers 2017, an unpublished study).

In 2020, US EPA evaluated the PWG pathology re-evaluation reports submitted by the registrant for the adrenal pheochromocytomas and thyroid C-cell tumors from the studies by Williams (1992) and Spicer (1985). US EPA (2020) accepted the findings of those pathology re-evaluation reports, with some modifications with regard to the total number of malignant pheochromocytomas in the 1 ppm dose group in Williams (1992).

In its 2020 re-assessment, US EPA performed its own statistical analyses of the data using Peto's prevalence test, and focused on the following issue: common spontaneous occurrence of adrenal pheochromocytomas.

As a result of this re-assessment, US EPA (2020) classified ethoprop as "Suggestive Evidence of Carcinogenic Potential," based on "the presence of one tumor type, thyroid C-cell tumors, which occurred in only one sex (males) and one species (F344 rat) and had no mutagenicity concerns."

US EPA's 1997, 1998, and 2020 assessments of the adrenal pheochromocytoma and thyroid C-cell tumor data from the studies in SD rats by Williams (1992) and F344 rats by Spicer (1985) are described in the sections below.

Adrenal pheochromocytoma in SD rats (Williams 1992)

US EPA 1997

In 1997 US EPA evaluated the adrenal pheochromocytoma tumor data from the male SD rat study of ethoprop by Williams (1992), and stated the following:

> "The primary concern was the occurrence of malignant pheochromocytomas of the adrenal gland in male Sprague-Dawley rats at all dose levels tested.
>
> At the high dose (400 ppm), the incidence (5/60, 8%) was significantly (p=0.005) higher than the concurrent controls (0/41, 0%) and exceeded the historical control range (0-1.7%).
>
> Malignant pheochromocytomas were seen in 2/16 males at the low-dose (1 ppm) and in 2/18 males at the mid dose (60 ppm). The Committee noted that while the adrenals of all high dose group rats were examined microscopically, only the adrenals of rats that died or were sacrificed moribund were examined from the low and mid dose groups. Because of this variation, the true dose-responsive nature of the tumor incidence could not be ascertained.
>
> The Committee attributed this tumor to treatment because: (i) it was seen at all dose levels, even at the low-dose (1 ppm) in the absence of cholinesterase inhibition; (ii) this malignant tumor is rare in rats and is life-threatening; and (iii) the incidences at the high dose exceeded both the concurrent control and the historical control range." (US EPA 1997a, p. 22)

US EPA 1998

In 1998 US EPA evaluated additional material submitted by the registrant regarding the adrenal malignant pheochromocytomas observed in the male rat study by Williams (1992), including historical control data.

With regard to the historical control data, US EPA stated in 1998:

> "Malignant pheochromocytomas exceeded the historical control range for the period of approximately 5 year preceding this study. However, the registrant submitted new historical control data from the testing lab for approximately 5 years after the study. In the new historical control data, pheochromocytomas in the present study had a similar incidence for 1 study while another study had an incidence above the current study. One study had decreased incidence compared to the present study and another study had zero malignant pheochromocytomas." (US EPA 2020, p. 9)

With regard to the spontaneous occurrence of adrenal malignant pheochromocytomas and the lethality of these tumors and progression of benign pheochromocytomas to malignancy in the male rat study by Williams (1992), US EPA stated in 1998:

> "Malignant adrenal pheochromocytomas are classified as "uncommon" tumors by the Society of Toxicologic Pathologist but should not be described as "life-threatening" as mentioned in the preceding Cancer Peer Review (CPR) document (5/9 animals with these tumors survived to study termination). Benign pheochromocytomas cannot be stated as progressing to malignancy, according to HED consulting pathologist, Dr. Luke Brennecke." (US EPA 2020, p. 9)

In 1998 US EPA reiterated that "The Committee's primary concern is still the occurrence of malignant adrenal pheochromocytomas which was seen at all dose levels tested. …." and re-affirmed the classification of ethoprop as a "likely" human carcinogen (US EPA, 2020, see pp. 8-10).

US EPA 2020

In 2020 US EPA evaluated the PWG pathology re-evaluation report for the adrenal pheochromocytomas from the male SD rat study by Williams (1992), and accepted the findings of the report, with some modifications to the total number of malignant pheochromocytomas in the 1 ppm dose group. US EPA also evaluated additional material submitted by the registrant on adrenal pheochromocytomas, including additional historical control data.

With regard to historical control data for adrenal malignant pheochromocytoma submitted by the registrant (US EPA 2020, p. 10 and Table 3 on p. 12), the US EPA considered data on the spontaneous occurrence in SD and SD-derived rats fed diet *ad libitum* from studies conducted in other laboratories: Baldrick (2005) reports data from "in house" Covance Laboratory studies; Chandra et al. (1992) reports data from American Cyanamid Company studies; and McMartin et al. (1992) reports data from Ciba-Geigy Corporation studies. OEHHA notes that the most informative historical

control data come from the same laboratory as the study being evaluated, not from other laboratories or facilities, and that in 1998, US EPA's consideration of historical control data was specific to data from the same test facility (see discussion above). Additionally, US EPA (2020, Table 3 indicates that data from studies that were conducted within 5 years prior to or 5 years after Williams (1992) were considered as historical control data. OEHHA notes that the in-life portion of the Williams (1992) studies began July 17, 1989 and ended July 24, 1991. Using these dates, studies starting no earlier than July 17, 1984 and ending no later than July 24, 1996 would have been eligible for consideration as providing historical control data. It is not clear from Table 3 in US EPA (2020) whether this timeframe was applied; the only mention by US EPA of a date associated with Williams (1992) is that it was "completed September 10, 1992" (US EPA 2020, p. 22).

In 2020 the US EPA concluded the following about the adrenal pheochromocytoma tumors observed in the male SD rat study of ethoprop by Williams (1992):

> "In Sprague-Dawley rats (Williams 1992; MRID 42530201), the results of HED's statistical reassessment of PWG tumor rates using the Peto's prevalence test showed that male rats had a statistically significant ($p < 0.05$) pairwise comparison only of the low (1 ppm) dose group with the controls for malignant adrenal pheochromocytomas. HED applied the Peto's Prevalence test because it adjusts for mortality unlike the statistics used by the registrant (e.g., Cochran-Armitage test). The Committee noted that the PWG only evaluated the low- and mid-dose animals that were available, not the total animals. The Committee also noted that there was no dose response relationship for this tumor type. The incidence of benign adrenal pheochromocytomas was within the range of appropriate historical control data. The CARC considered only the historical control data from studies that included *ad libitum* feeding, and that encompassed the actual study date (i.e., conducted within 5 years prior to or 5 years after the study being evaluated). These studies included Baldrick (2005), McMartin et al. (1992), and Chandra et al. (1992). In contrast, the incidence of malignant adrenal pheochromocytomas was outside the range of appropriate historical control data for all doses tested (i.e., 0 – 6.7% reported by Baldrick 2005; 0 – 6% reported by McMartin et al. 1992). In addition, the incidences of pre-neoplastic lesions (e.g., adrenal medullary hyperplasia) do not support a treatment-related effect. The CARC did not consider the adrenal tumors to be treatment-related." (US EPA 2020, p. 26)

Thyroid C-cell tumors in SD rats (Williams 1992)

US EPA 1997

In 1997 US EPA evaluated the thyroid C-cell tumor data from the male SD rat study of ethoprop by Williams (1992), and stated the following:

> "The Committee also had concern for the occurrence of C-cell tumors of the thyroid glands in two strains of male rats; Sprague-Dawley and Fisher 344 (in two different studies).
>
> In Sprague-Dawley rats, the incidences of C-cell carcinomas at the high dose (3/66, 5%) showed a positive trend (p = 0.014), pair-wise significance (p = 0.042) when compared to controls (0/61, 0%) and exceeded the historical control range. Of the 7 studies conducted at the testing laboratory, C-cell carcinomas were seen in 1/50 (2%) rats in one study and in 1/60 (1.7%) rats in another study but none in 5 studies consisting of 330 rats. Thus, the incidence (5%) of this tumor seen in the present study was more than twice that seen in seven previous studies." (US EPA 1997a, p. 22-23)

In 1997 US EPA stated the following regarding thyroid C-cell tumor findings from three studies in male rats:

> "(ii) occurrence of another type of tumor (C-cell carcinomas of the thyroid glands) in male rats in two strains (Sprague-Dawley and Fischer 344) in three different studies at doses that did cause cholinesterase inhibition" (US EPA 1997a, p. 25)

US EPA 1998

In 1998, US EPA:

> "noted that the incidence of [thyroid] C-cell carcinomas at the high dose (400 ppm) in [male] SD rats showed a positive trend, reached pair-wise significance when compared to controls, and exceeded the historical control range (Table 5). The CARC 1998 report did not present the historical control data but stated that the historical control data are in a file copy. The CARC also noted that in the Spicer (1985) study (MRID 40291801) in [male] Fischer 433 rats, while positive trends were seen for C-cell adenomas, carcinomas, and combined adenomas/carcinomas, there was a non-statistically significant increase in C-cell carcinomas at the high dose (100 ppm) in males when compared to zero in the concurrent controls (Table 7). The CARC concluded that the increase in C-cell carcinomas in this strain of rats is supportive of the same target organ/tumor type in the Sprague-Dawley rats." (US EPA 2020, p. 14).

US EPA 2020

In 2020 US EPA evaluated the PWG pathology re-evaluation report for the thyroid C-cell tumors from the male SD rat study by Williams (1992) and accepted the findings of the report. US EPA also evaluated additional material submitted by the registrant on thyroid C-cell tumors, including additional historical control data.

With regard to historical control data for thyroid C-cell tumors in SD rats submitted by the registrant (see US EPA 2020) (Table 10 on p. 19), the US EPA considered data on the spontaneous occurrence in SD and SD-derived rats fed diet *ad libitum* from studies conducted in other laboratories: Baldrick (2005) reports data from "in house" Covance Laboratory studies; Chandra et al. (1992) reports data from American Cyanamid Company studies; McMartin et al. (1992) reports data from Ciba-Geigy Corporation studies. OEHHA notes that the most informative historical control data come from the same laboratory as the study being evaluated, not from other laboratories or facilities. (See also the previous discussion on study start and ending dates for Williams (1992) and historical control studies).

In 2020 the US EPA concluded the following about the thyroid C-cell tumors observed in the male SD rat study of ethoprop by Williams (1992):

> "In Sprague-Dawley rats (Williams 1992; MRID 42530201), the results of the CARC's reassessment of the PWG tumor rates indicated that male rats had a statistically significant trend for thyroid C-cell carcinomas. The Committee noted that the incidence of thyroid C-cell carcinomas at the high dose (400 ppm) was outside the range of appropriate historical control data (i.e., Baldrick 2005; McMartin et al. 1992; Chandra et al. 1992), but there was no pairwise statistically significant difference in comparison to concurrent controls. For thyroid C-cell carcinomas, Baldrick (2005) reported an historical control range of 0 – 3.4%; whereas the range report[ed] by McMartin et al. (1992) was 0 – 2.9%). Chandra et al. (1992) did not present a range of historical control data but did provide a mean rate of 0.82%. Also noted was that the high dose (400 ppm) was excessive based on several factors: (1) the high dose had to be reduced from 600 ppm to 400 ppm after 2 weeks of dosing due to excessive toxicity in females (tremor, ataxia, and 2 deaths); (2) brain ChE activity in 400 ppm males was decreased 64% compared to controls at study termination; (3) there were body weight decrements of -20% compared to controls during the first half of the study; (4) neurotoxicty was noted in a subchronic neurotoxicity study at the same dose (400 ppm); (5) the 400 ppm dose is about 2/3 of the LD_{50} dose for ethoprop; and (6) ethoprop has a steep dose-response curve with death occurring at dose levels slightly above those causing clinical signs. Therefore, the CARC did not

consider these tumors treatment related at any dose tested." (US EPA 2020, p. 26-27)

Thyroid C-cell tumors in F344 rats (Spicer 1985)

US EPA 1997

In 1997 US EPA evaluated the thyroid C-cell tumor data from the male F344 rat study of ethoprop by Spicer (1985), and stated the following:

> "The Committee also had concern for the occurrence of C-cell tumors of the thyroid glands in two strains of male rats; Sprague-Dawley and Fisher 344 (in two different studies).
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> In the 1985 Fischer 344 rat study, a positive trend was seen for C-cell adenomas (p=0.036), carcinomas (p=0.020), and combined adenomas/carcinomas (p=0.005) of the thyroid glands. The Committee noted the presence of C-cell carcinomas in 3 of 50 rats (6%) at the high dose (100 ppm) when compared to none in the concurrent controls. Historical control incidences from the testing laboratory were not available. The increase in C-cell carcinomas seen in this strain of rats is supportive of the same target organ/tumor type in the Sprague-Dawley rats." (US EPA 1997a, p. 23)

As noted previously, US EPA stated the following regarding thyroid C-cell tumor findings from three studies in male rats:

> "(ii) occurrence of another type of tumor (C-cell carcinomas of the thyroid glands) in male rats in two strains (Sprague-Dawley and Fischer 344) in three different studies at doses that did cause cholinesterase inhibition" (US EPA 1997a, p. 25)

US EPA 1998

In 1998, "[t]he CARC (1998) assessment noted that male rats in the Spicer (1985) feeding study (MRID 40291801) exhibited a statistically significantly increasing trend for thyroid C-cell adenomas, carcinomas, and combined tumors (Table 7)." (US EPA 2020, p. 15)

US EPA 2020

In 2020 US EPA evaluated the PWG pathology re-evaluation report for the thyroid C-cell tumors from the male F344 rat study by Spicer (1985) and accepted the findings of

the report. US EPA also evaluated additional material submitted by the registrant on thyroid C-cell tumors, including additional historical control data.

With regard to historical control data for thyroid C-cell tumors in F344 rats submitted by the registrant (see US EPA 2020, Table 10 on p. 19), the US EPA considered data on the spontaneous occurrence in F344 rats fed diet *ad libitum* from studies conducted in other laboratories: Haseman et al. (1998) reports data from National Toxicology Program studies; Lang (1990) reports data from Charles River Laboratories studies. OEHHA notes that the most informative historical control data come from the same laboratory as the study being evaluated, not from other laboratories or facilities. OEHHA notes that the in-life portion of the Spicer (1985) studies began September 14, 1982 and ended between September 11-19, 1984. Using these dates, studies starting no earlier than September 11, 1977 and ending no later than September 19, 1989 would have been eligible for consideration as providing historical control data. It is not clear from Table 10 in US EPA (2020) whether this timeframe was applied; the only mention by US EPA of a date associated with Spicer (1985) is that it was "issued April 30, 1985" (US EPA 2020, p. 20).

In 2020 the US EPA concluded the following about the thyroid C-cell tumors observed in the male F344 rat study of ethoprop by Spicer (1985):

> "In the F344 rats (Spicer 1985; MRID 40291801), the results of the CARC's reassessment of tumor rates revealed that male rats had statistically significant trends for both thyroid C-cell adenomas and thyroid C-cell adenomas and/or carcinomas combined. There was also a statistically significant pair-wise comparison of high dose (100 ppm) group with the controls for thyroid C-cell adenomas and/or carcinomas combined. The Committee commented that the significant trend and pairwise comparison at the high dose for the combined adenomas/carcinomas was driven by the incidence of adenomas. The Committee noted that the incidences of thyroid C-cell adenomas and carcinomas were within the historical control range reported by Haseman (1998). Haseman (1998) reported the mean rates and range of historical control data for thyroid C-cell adenoma as 13 (range: 2 – 35%) and for thyroid C-cell carcinoma as 1.8 (range: 0 – 6%). However, the thyroid C-cell carcinomas were outside the historical control range (0 – 2.8% for carcinomas; 0 – 6.4% for adenomas) in the Lang (1990) study. The Committee also discussed the Spicer (1985) study and concluded that the 100 ppm (high dose) was not excessive; cholinesterase activity was decreased by 68% (in brain) and by 86% (in red blood cell) but there was no mortality or serious clinical signs of toxicity. The Committee also mentioned that in this case there were no significant thyroid non-neoplastic effects (e.g., hyperplasia) that would support a carcinogenic effect. However, the

CARC concluded that the statistically significant increase in thyroid C-cell tumors in the high-dose male F344 rats is treatment-related." (US EPA 2020, p. 27)