Draft RoC Monograph on Pentachlorophenol and By-Products of its Synthesis

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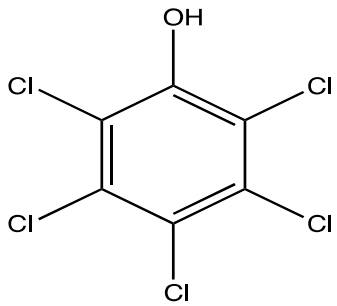
Rationale and human exposure

Pentachlorophenol was selected as a candidate substance



- Evidence of past and present widespread exposure
  - Pesticide
    - 1936-1984: Ubiquitous commercial and residential use as a wood preservative, multipurpose biocide.
    - From 1987 use restricted; Now registered only for wood preservation; restricted to commercial use, i.e., utility poles and cross arms, railroad ties, laminated wood, wharf pilings
- Numerous studies in experimental animals and humans and some reviews
  - IARC (1999) review of chlorophenols
    - Limited evidence in humans; since review, several cohort studies have been published.
  - US EPA IRIS report (2010) on pentachlorophenol (doesn't include by-products of synthesis)
    - 'Likely carcinogenic to humans' based on strong evidence for NHL and multiple myeloma, additional cohort studies were not included in review.

Preparation of Draft Monograph on Pentachlorophenol and By-Products of its Synthesis

Relied on two forums to get information: Public webinar and a government information group:

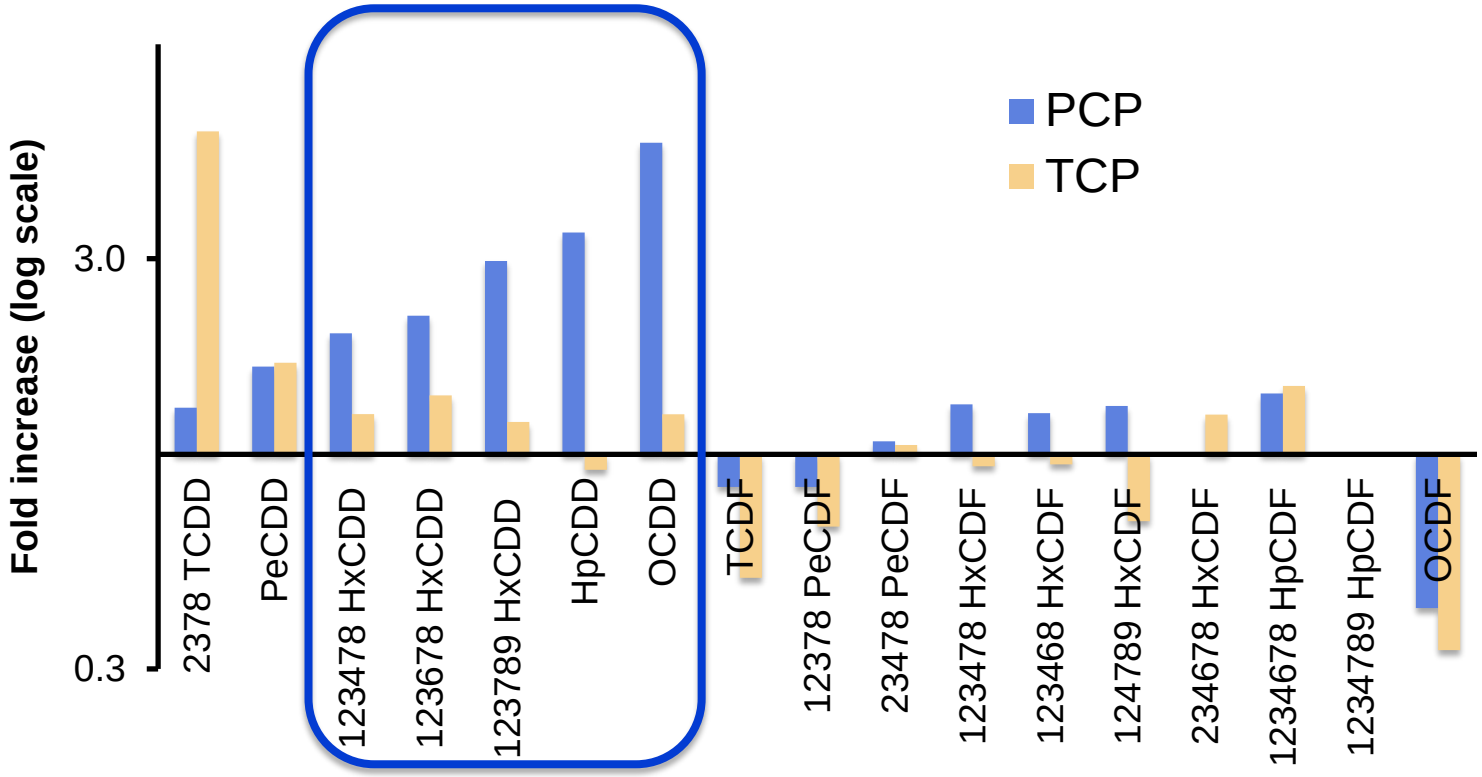
Objective: Differentiate potential cancer effects of PCP exposure from effects due to occupational co-exposures or PCP contaminants

- Public webinar on human epidemiology studies
  - Discussions on what chemicals people are exposed to led to clarifying the candidate substance
  - Received public and technical input from experts in the field
- Information group on cancer studies in experimental animals
  - Discussion of potential effects of pentachlorophenol and individual by-products and cumulative effect of dioxin-like by-products
  - Received input from government toxicologists and dioxin experts

‘Pentachlorophenol and By-Products of its Synthesis’

- By-products of its synthesis make up 10% of commercial pentachlorophenol
- By-products of pentachlorophenol synthesis include:
  - Lesser chlorinated phenols (tri-, tetra-)
  - Hexachlorobenzene
  - Dioxins and furans; primarily hexa-, hepta-, octa- dioxin and furan congeners
- 2,3,7,8-TCDD considered a contaminant
  - Not produced during pentachlorophenol synthesis by direct chlorination of phenol.
  - Rarely detected in commercial pentachlorophenol preparations.
- Cancer study databases on pentachlorophenol and by-products
- Previous pentachlorophenol exposure can be assessed from fingerprint of hexa-, hepta-, octa-dioxin congeners.

Dioxins found among PCP production workers differ from trichlorophenol (TCP) production workers



Dioxins associated with PCP exposure are the higher chlorinated dioxins (HxCDD, HpCDD and OCDD)

Lipid adjusted dioxins measured in TCP or PCP workers 20 years after exposure (Collins *et al.* 2008)

Similar dioxins found in PCP exposed people or animals in other studies

Different geographical locations and occupations

Study	4 Hx CDD	6 Hx CDD	9 Hx CDD	Hp CDD	OCDD	TCDD	PCDD	TCDF	Pe CDF*	Hx CDF*	Hp CDF*	OCDF
US PCP Producers	++	++	+++	++++	+++++	<1.5	+	inv.	< 1.5	<1.5	<1.5	inv.
NZ Sawmill Workers	<1.5	++	+	++	++	<1.5	< 1.5	NR	NR	NR	NR	NR

Environmental exposure

Study	4 Hx CDD	6 Hx CDD	9 Hx CDD	Hp CDD	OCDD	TCDD	PCDD	TCDF	Pe CDF*	Hx CDF*	Hp CDF*	OCDF
US Env wood plant	<1.5	<1.5	+	+++	+++	inv.	inv.	<1.5	inv.	<1.5	<1.5	<1.5
PCP Cattle (pg/g fat)**	10	102	11	328	331	0	6.1	0	2.4	25	50	73

Virtually everyone who is exposed to PCP is also exposed to its by-products

Fold increased of lipid adjusted dioxins compared to reference: < 1.5, + = 1.5 to 1.9, ++ = 2.0 to 2.5, +++ = 2.5 to 2.9, ++++ = 3 to 4.9, +++++ = 5 or greater; inv.= inverse relationship, higher in reference group; NR= not reported

* Sum of dioxin congeners

**No reference group available for PCP exposed cattle, measured levels are reported

References: PCP producers (Collins 2008); NZ sawmill workers (McLean 2009); US env (Dahlgren 2007); PCP cattle (Huwe 2004)

Exposure: Key Questions

- Is there significant exposure of pentachlorophenol and by-products of its synthesis to persons living in the United States?
  - Exposure can be inferred from data on usage, production, or evidence for exposure in the workplace, from the environment or consumer products, diet, or other sources due to lifestyle choices (such as tobacco smoking).

- How are people (sources, settings, and levels) exposed to the candidate substance?

Significant number of persons living in the U.S. are exposed to pentachlorophenol and by-products of its synthesis

- Widespread exposure, both past and present
  - Current exposures are lower than in the past, but exposure to workers and to general public still occurs
  - Evidence of recent exposures in the general population
    - People and homes near wood treatment facilities; blood levels of pentachlorophenol exposure: dioxin fingerprint from people near wood treatment facilities
    - From environmental and biological samples taken from preschool children and from their homes and day care centers
    - Data from the National Health and Nutrition Examination Survey (NHANES)
    - Low levels of pentachlorophenol have been found in foods, water, air, dust, and soil
    - Toxics Release Inventory (2011): 96,000 lbs from 30 U.S. facilities
  - Exposure to general population is primarily by inhalation and ingestion

Significant number of persons living in the U.S. are exposed to pentachlorophenol and by-products of its synthesis

- Occupational exposure
  - Workers who formulate pentachlorophenol for use, or treat or come into contact with treated lumber, e.g., sawmill workers, utility linemen
  - Urinary levels of pentachlorophenol in workers from wood treatment plants
  - Blood levels of dioxin congener fingerprint in former production workers (20 years after employment)
  - Exposure from treating lumber is primarily dermal; inhalation exposure can occur from pentachlorophenol processing and pressure-treatment of wood

Pentachlorophenol and By-Products of its Synthesis Properties and Human Exposure

Questions or Clarifications?

Pentachlorophenol and By-Products of its Synthesis Properties and Human Exposure

- Comment on whether the chemical identity and description of pentachlorophenol (Section 1: Properties and Human Exposure) are clear and technically accurate.
- Comment on whether the information on use, production, and human exposure for pentachlorophenol (Section 1: Properties and Human Exposure and Appendix B) is clear and technically accurate.
  - Identify any information that should be added or deleted.
- Comment on whether adequate information is presented to document past and/or current human exposure to pentachlorophenol in the United States. Exposure can be inferred from data on usage, production, or evidence for exposure in the workplace, from the environment or consumer products, diet, or other sources due to lifestyle choices (such as tobacco smoking).

Draft RoC monograph on pentachlorophenol and by-products of its synthesis

Cancer studies in experimental animals

Key Questions: Studies in Experimental Animals

- What is the scope of the literature?
- What are the tissue sites?
- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of pentachlorophenol from studies in experimental animals?

Cancer studies in experimental animals: Methods

- Literature search to identify animal cancer studies (Appendix A)
- Development of Assessment protocol
- Assessment of reporting and study quality (Appendix D)
  - Adequacy of reporting quality: Adequate information to assess study quality for key elements?
  - Study quality
    - Conclusions reached on the level of concerns about the following performance elements: Substance characterization, animal husbandry, study design, endpoint assessment, and data interpretation
  - Overall assessment of study quality and utility to inform the cancer evaluation
  - Assessment of neoplasm findings: integration across studies
  - Identification of exposure-related tissue sites
- Preliminary level of evidence conclusion based on RoC criteria

Cancer studies in experimental animals: Database overview

- Cancer studies in rats and mice
- Study designs varied: chronic cancer studies, co-carcinogen, mechanistic-pentachlorophenol (PCP) as enzyme inhibitor; short-term studies: gene knockout and transgene studies
- Grade of PCP varied: technical grade, Dowicide EC-7, 99% pure
- Rats: four studies, dietary exposure, using three strains of rat
  - NTP studies considered to be most informative
- Mice: seven studies, dietary exposure, using five strains of mice
  - NTP studies considered to be most informative
- One dermal study using Tg.AC transgenic mice
- All studies in experimental animals were considered adequate for study quality evaluation.

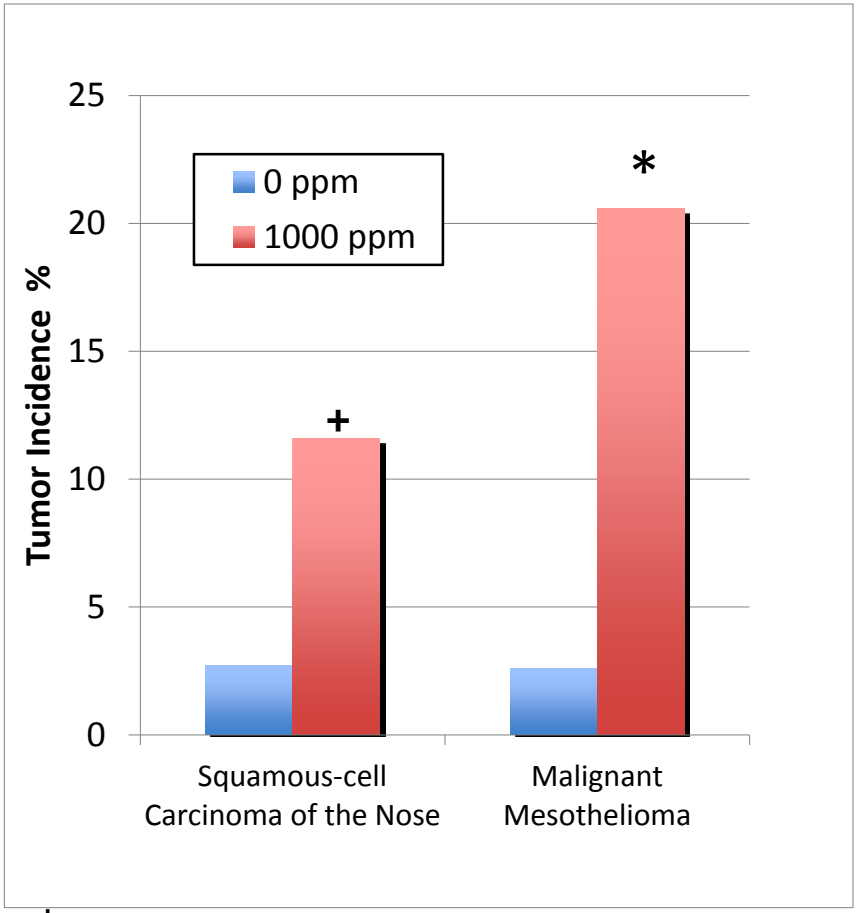
Pentachlorophenol exposure causes cancer in rats

NTP bioassay (99% PCP, feed)

- Study Designs
  - 2 yr, continuous exposure
    - Dose (ppm): 0, 100, 200, 400, 600 (50 animals/group, M & F)
  - 1 yr, stop exposure, 2 yr duration
    - Dose (ppm): 0, 1000 (50 animals/group, M & F)
- Strengths
  - Sufficient # animals, chemical characterization, dose selection to induce mild toxicity, sufficient study duration, complete histopathology and reporting

NTP 1999, Chhabra 1999

Stop Exposure Study: F344/N Male Rats



+ Rare tumor; incidence exceeded historical control (HC) range of 0-4%; * P ≤ 0.05; HC range malignant mesothelioma = 0- 8%

Other studies in rats

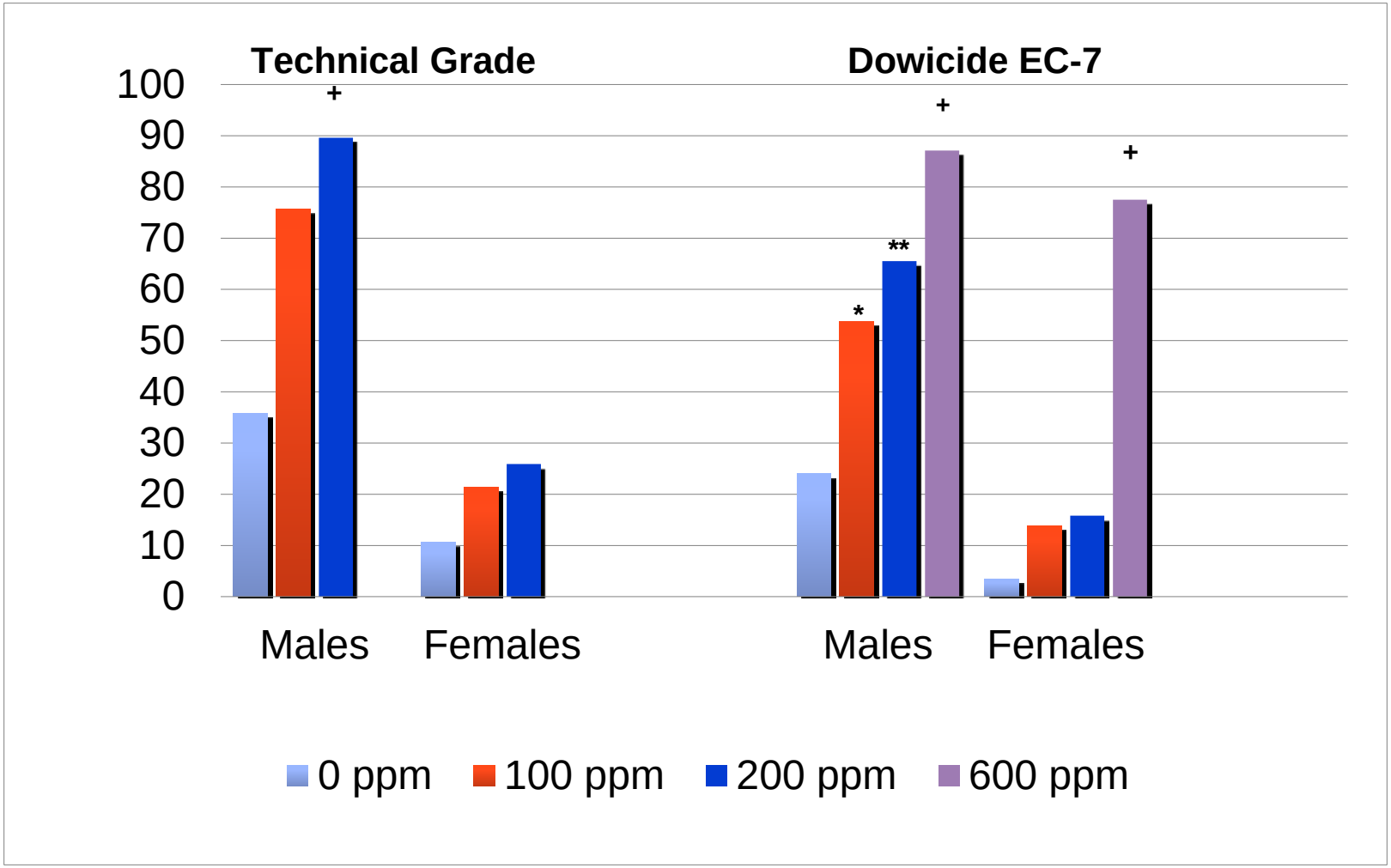
- Studies in rats with limited quality
  - One cancer study using Dowicide EC-7 in feed (Schwetz 1978)
  - One co-carcinogen study using technical grade PCP in feed (Mirvish 1991)
- Findings
  - Cancer study negative (total tumors)
  - Co-carcinogen study positive for hepatomas in females, possibly due to TCDD/TCDF contamination
- Limitations include
  - Inadequate number of animals per dose group
  - Inadequate pathology: gross examination only
  - Inadequate reporting: total tumors only reported; number of animals not reported
  - Limited or no chemistry on test article

Cancer studies in mice: Informative studies

NTP bioassays (B6C3F1 mice, feed)

- Study Designs
  - Technical grade, 2 yr, continuous exposure
    - Dose (ppm): 0, 100, 200 (50 animals/group, M & F)
  - Dowicide EC-7, 2 yr, continuous exposure
    - Dose (ppm): 0, 100, 200, 600 (50 animals/group, M & F)
- Strengths
  - Sufficient number of animals
  - Chemical characterization
  - Dose selection to induce mild toxicity
  - Sufficient study duration
  - Complete histopathology and reporting

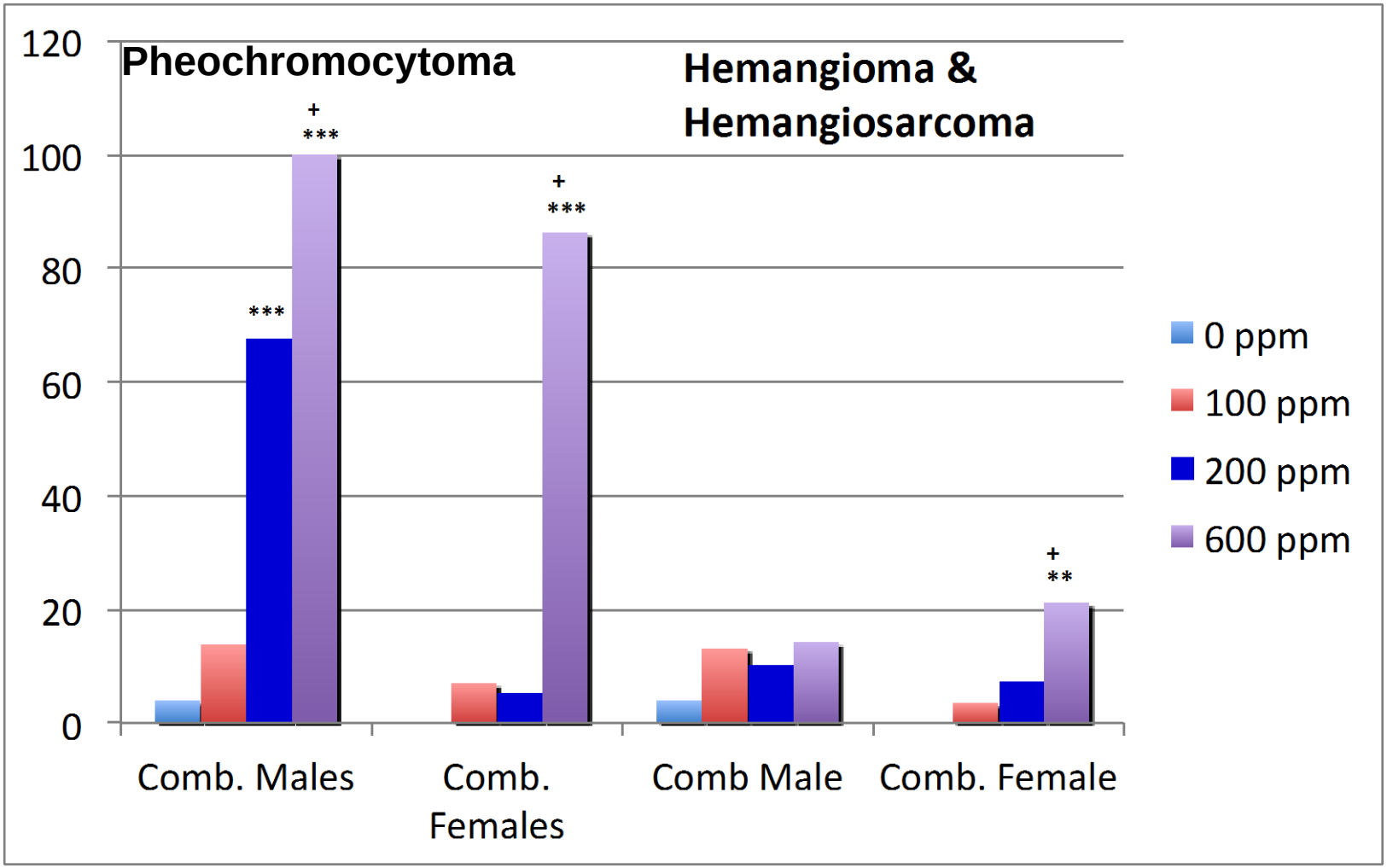
Percent Incidence of combined hepatocellular tumors in B6C3F$_1$ mice



*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$; +$P_{trend} \leq 0.001$

NTP 1989, McConnell 1991

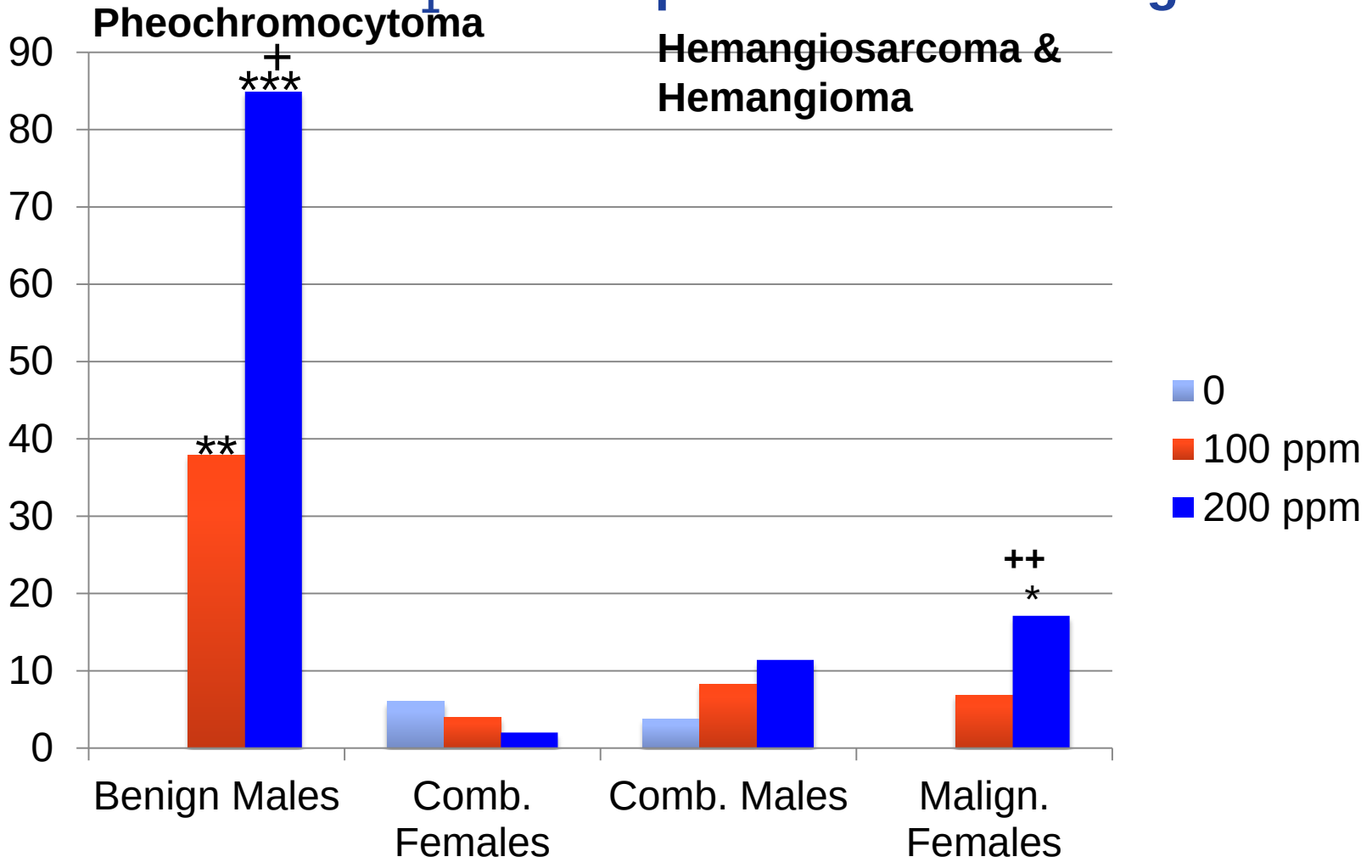
Percent Incidence of adrenal gland and blood vessel tumors in B6C3F$_1$ mice exposed to Dowicide EC-7



*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$; +$P_{trend} \leq 0.001$

NTP 1989, McConnell 1991

Percent incidence of adrenal gland and blood vessel tumors in B6C3F$_1$ mice exposed to technical grade PCP



*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$; +$P_{trend} \leq 0.001$, ++$P_{trend} = 0.024$

NTP 1989, McConnell 1991

Other studies in mice

- Studies in mice with limited quality
  - 1 cancer study using Dowicide-7 in feed, 2 strains of mouse (Innes 1969)
  - 2 mechanism studies using pure PCP in feed (Boberg 1983, Delclos 1986)
  - 2 cancer screening studies using pure PCP in genetically modified mice – feeding Trp53(+/-) and dermal (Tg•AC) (Spalding 2000)
- Findings
  - No exposure-related tumors observed in all studies except for liver tumors in v-*ras*^{Ha} transgenic Tg.AC mice
- Limitations
  - Limited histopathological examination
  - Short duration, low number of animals per dose groups
  - Tg.AC - problem with false positives; relevance of reporter gene activation mechanism underlying this model to mechanisms of human cancer is unclear

Studies in Experimental Animals: Preliminary Recommendation

There is sufficient evidence of carcinogenicity of pentachlorophenol and by-products of its synthesis in experimental animals, based on increased incidence of malignant and/or a combination of malignant and benign tumors in rats and mice or at multiple tissue sites.

- Statistically significant increases in malignant mesothelioma of the **tunica vaginalis** in male rats.
- Non-significant increases greater than historical controls in rare **nasal cavity** squamous-cell carcinoma in male rats.
- Statistically significant increases in **liver** tumors and **adrenal gland** tumors in both sexes and tumors of **blood vessels** in female mice.

Studies in Experimental Animals

Questions or Clarifications?

Studies in Experimental Animals

- Please comment on the overall approach for preparing the cancer assessment of the studies in experimental animals. Specifically, are the methods for evaluating study quality reasonable, transparent, and clearly presented? Is the assessment of the utility of the studies for informing the cancer evaluation systematic, transparent, and clearly presented?
- Comment on whether the scientific information from cancer studies in experimental animals for pentachlorophenol (Section 4: Studies of Cancer in Experimental Animals and Appendix D) is clear, technically correct, and objectively presented.
  - Identify any information that should be added or deleted.
- Provide any scientific criticisms of NTP's cancer assessment of the experimental animal studies of exposure to pentachlorophenol and how the scientific evidence across studies was synthesized.

Draft RoC monograph on pentachlorophenol and by-products of its synthesis

Disposition and mechanisms

Mechanistic and other relevant data support the carcinogenicity of pentachlorophenol

- Disposition and metabolism of pentachlorophenol in rodents and humans
- Evidence that genotoxicity of pentachlorophenol is mediated by its metabolites
- Pentachlorophenol metabolites and dioxin-like synthetic by-products contribute to carcinogenicity
- Potential modes of action of pentachlorophenol exposure and the development of non-Hodgkin lymphoma, a major human cancer site.

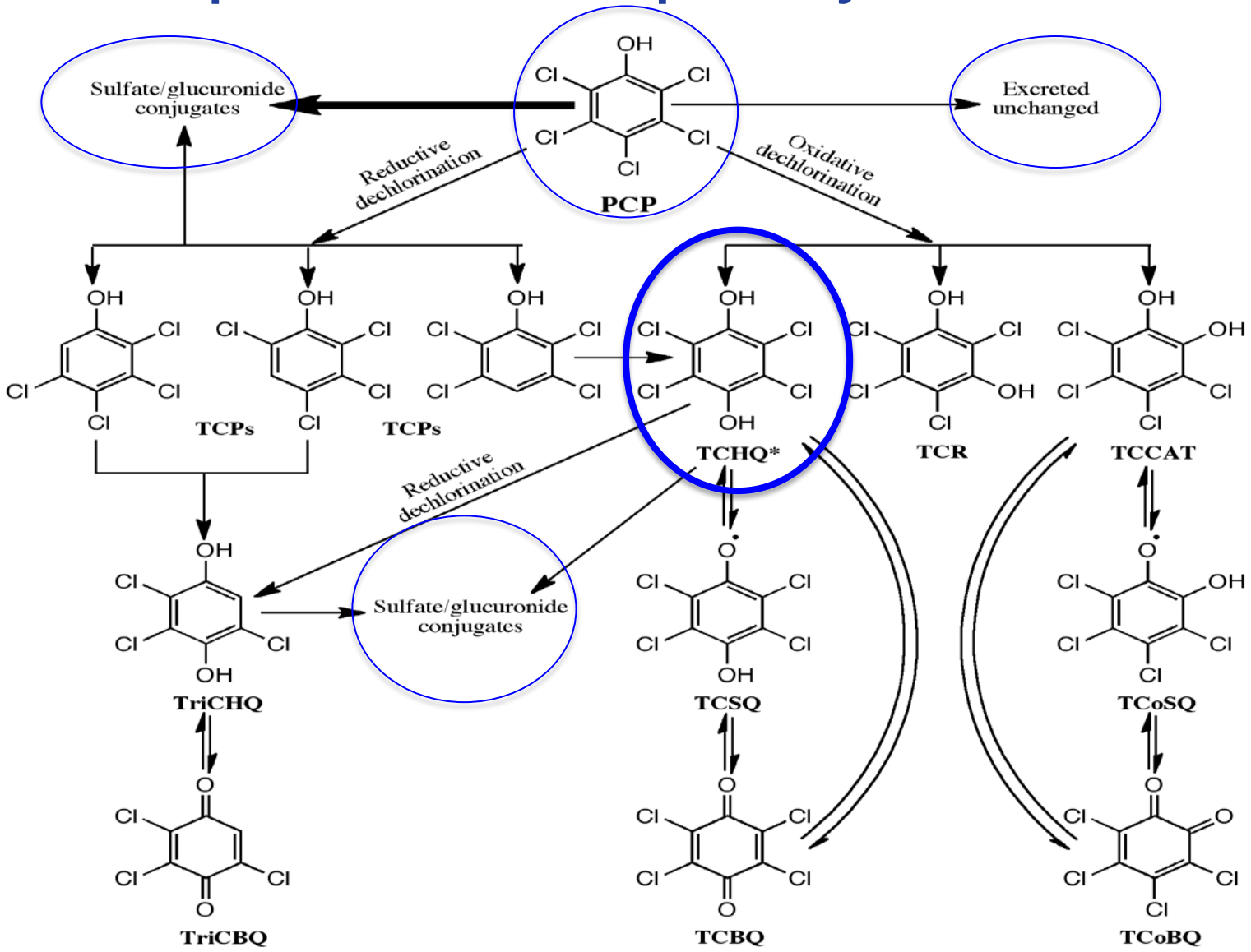
Mechanistic Data – Scope of literature for pentachlorophenol (PCP)

- Metabolism
  - Numerous metabolism studies in experimental animals
  - Human data limited to measurement in urine of PCP or PCP conjugate in occupational and non-occupational exposed workers, volunteers, and general population
  - Limited information on P450s: *Saccharomyces cerevisiae* expressing human CYP3A4 and rat microsomes treated with inducers of CYP2B2, CYP1A2, CYP3A1 metabolized PCP to tetrachlorohydroquinone
- Mechanistic studies
  - Extensive genetic toxicology database for PCP from *in vitro* studies: bacteria, non-mammalian eukaryotes, mammalian cells; few studies in rodents
  - Limited human data: Three studies with occupational exposure to PCP and measurement of chromosomal aberrations and/or sister chromatid exchanges

Disposition and Metabolism

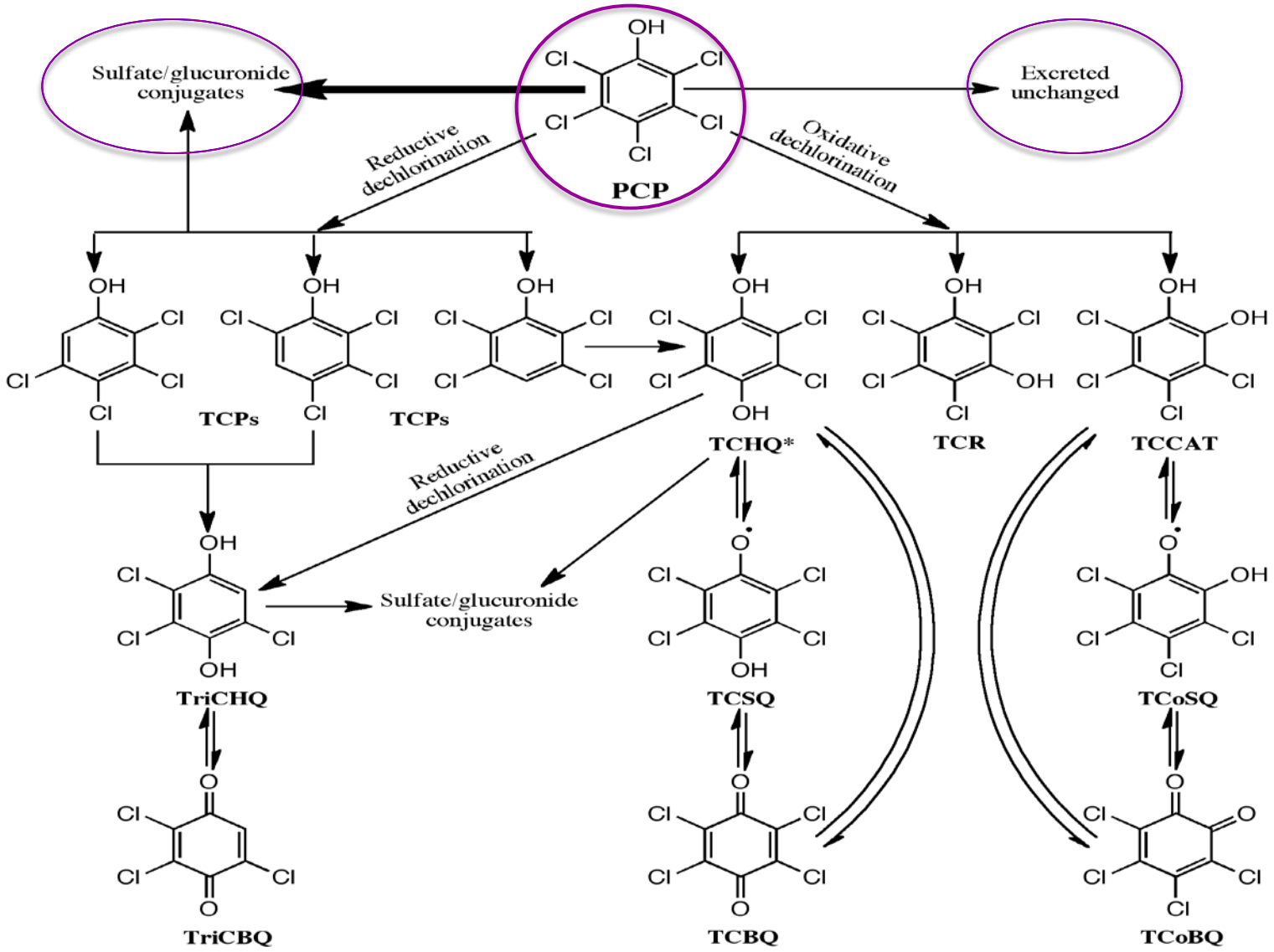
- Efficiently absorbed with dermal, oral, inhalation exposure; widely distributed, accumulation in tissues limited by extensive binding to plasma proteins
- Excreted primarily in urine; interspecies variation in metabolism-clearance slower and excretion half-life longer in humans vs. rats
- Rodent-urine: pentachlorophenol, sulfate or glucuronide conjugates, tetrachlorohydroquinone (TCHQ)
- Human-urine: pentachlorophenol, glucuronide conjugates
  - Human liver microsomes metabolize pentachlorophenol to pentachlorophenol glucuronide and TCHQ
  - Low levels of TCHQ detected in workers exposed to PCP and other chlorophenols and in urine samples from general population

Pentachlorophenol metabolic pathways



Sources: ATSDR 2001, Lin *et al.* 2002, Renner and Hopfer 1990a, Tsai *et al.* 2001

Pentachlorophenol metabolic pathways



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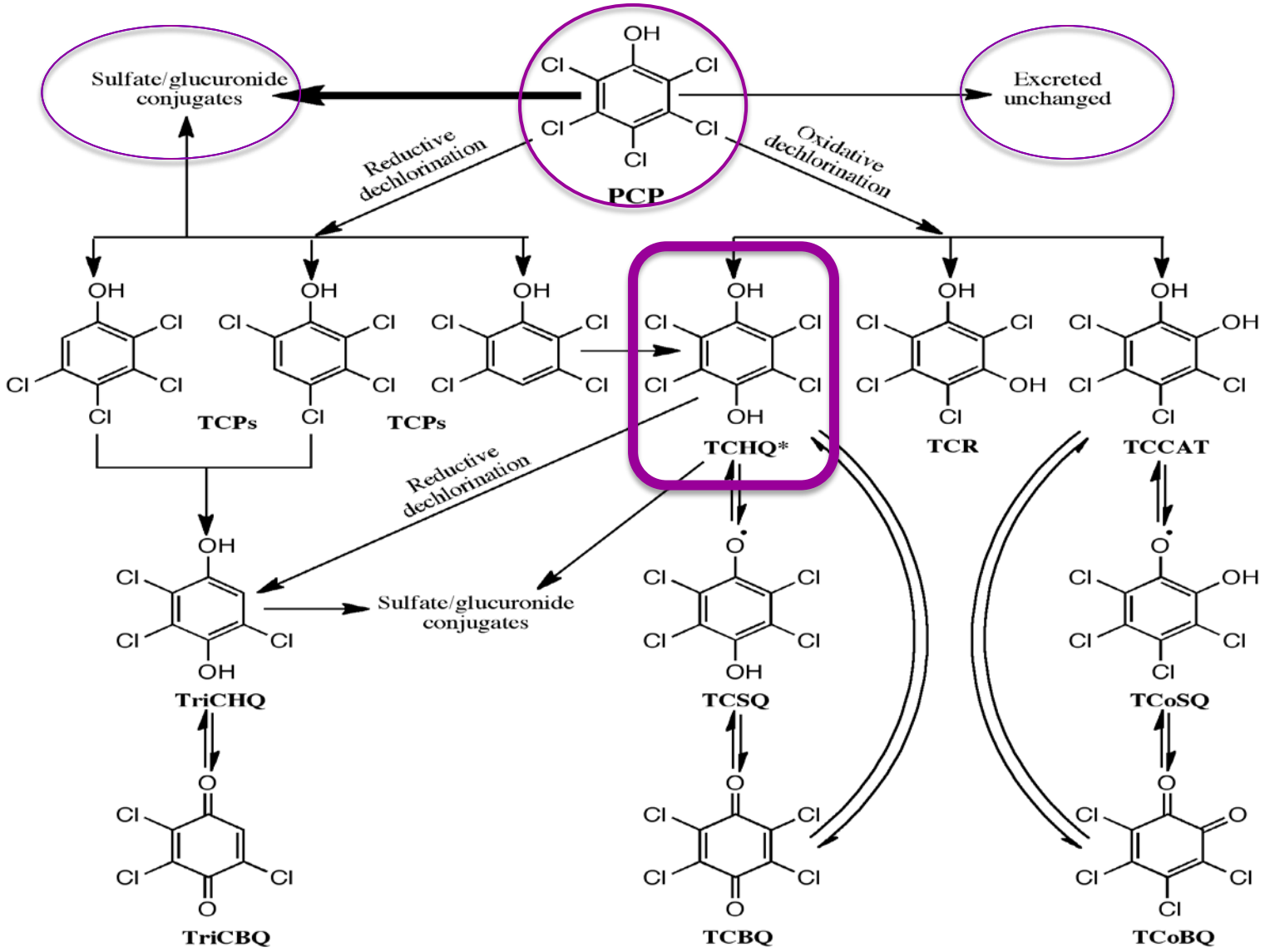
Pentachlorophenol metabolic pathways

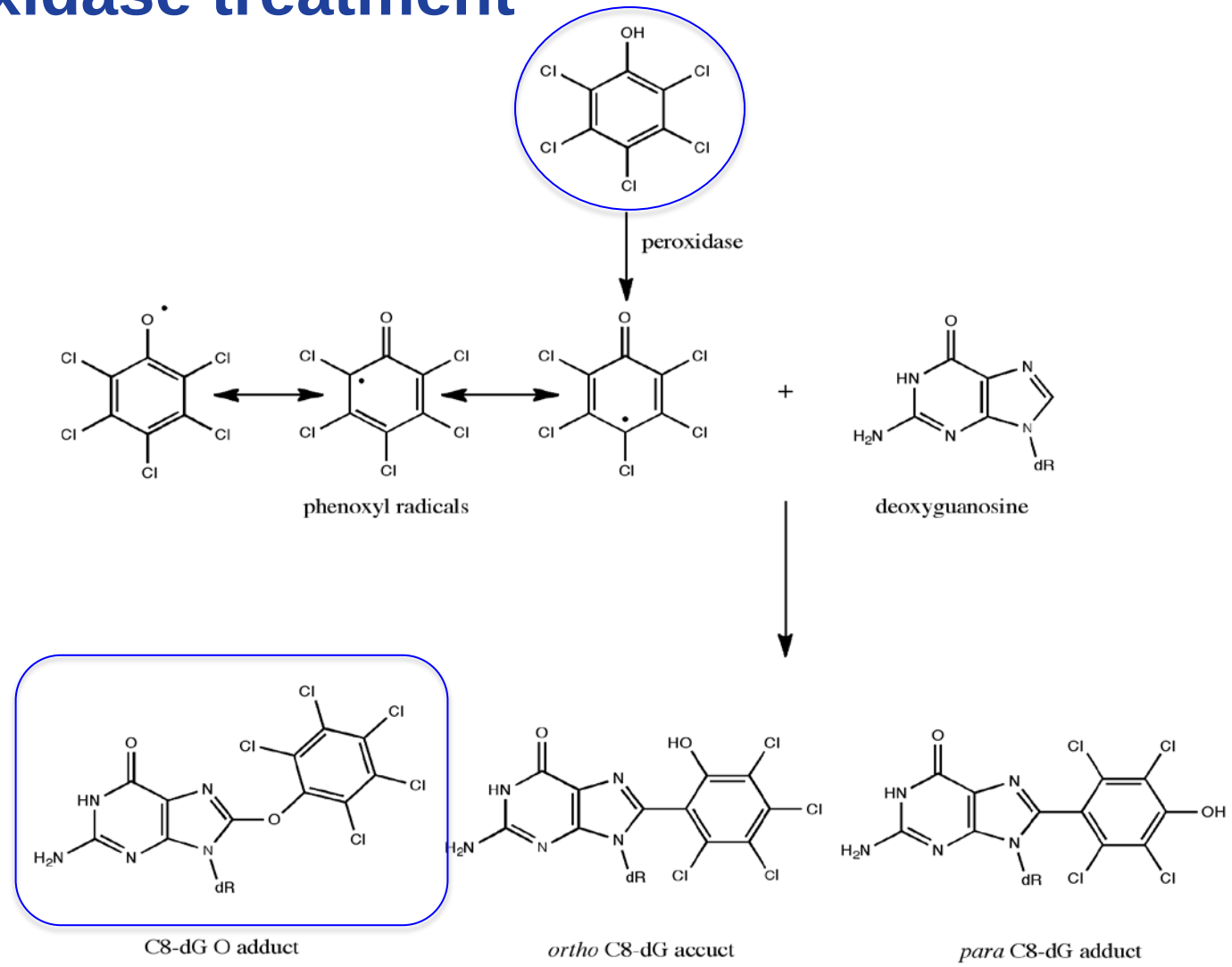


Sources: ATSDR 2001, Lin *et al.* 2002, Renner and Hopfer 1990a, Tsai *et al.* 2001

Genotoxicity of pentachlorophenol is mediated by its metabolites (Appendix E)

- Pentachlorophenol (PCP)
  - Induction of DNA damage in cells with metabolic capability (e.g., PBL, Hep-G2) and in metabolically incompetent cells (e.g., fibroblasts, HeLa cells, V79 cells) in the presence of exogenous metabolic activation
  - Evidence of induction of chromosomal damage and apoptosis in cells with metabolic capability
  - Evidence of C8-dG O-adducts in rodents
  - Limited evidence of chromosomal aberrations in exposed workers
- PCP metabolites are genotoxic and mutagenic
  - TCHQ is mutagenic; TCHQ and TCBQ are positive for DNA damage and DNA adducts
  - Hepatic and extrahepatic peroxidases form phenoxyl free radicals, O-bonded C8 dG DNA adducts, cause DNA and chromosomal damage and induce mutations.
    - Peroxidases and myeloperoxidases are present in bone marrow and lymphocytes; mechanism relevant to cancers of white blood cells.

Pentachlorophenol will form DNA adducts with peroxidase treatment



modified from Dai *et al.* 2005

Pentachlorophenol exposure: non-Hodgkin lymphoma

- Non-Hodgkin lymphoma (NHL) is associated with immunosuppression
- Pentachlorophenol exposure is linked to immunosuppression
  - Apoptosis observed in ‘pure’ PCP-exposed human lymphocytes and Jurkat T cells in culture
  - People exposed to PCP-containing pesticides: PCP blood levels and suppression of both cellular and humoral immunity.
  - Pure PCP and technical grade immunosuppressive to human lymphocytes affecting both cell-mediated and humoral immunity
    - Studies in mice: Dioxin/furan component of technical grade PCP immunosuppressive
- Dioxins interact with aryl hydrocarbon receptor (AhR) which affects numerous downstream biochemical pathways; immunosuppression by dioxins is believed to be mediated by activation of this receptor.

Disposition and Mechanisms: Summary

- Mechanistic data demonstrate biological plausibility for human cancers
- Proposed modes of action include metabolism to genotoxic and mutagenic metabolites, DNA damage (strand breaks), DNA adduct formation, chromosome aberrations and chromosome breakage, immunosuppression, and inhibition of apoptosis.
- Pentachlorophenol exposure causes biological effects similar to what occurs with NHL: immunosuppression and DNA damage (strand breaks), chromosome breakage, and inhibition of apoptosis.

Pentachlorophenol and By-Products of its Synthesis: Disposition and Mechanisms

Questions or Clarifications?

Pentachlorophenol and By-Products of its Synthesis: Disposition and Mechanisms

- Comment on whether the information on Disposition and Toxicokinetics (Section 2) is clear and technically correct, and objectively presented.
  - Identify any information that should be added or deleted.
- Comment on whether the genotoxicity and other mechanistic data (Section 5: Mechanistic Data and Other Relevant Effects and Appendix E and F) presented in the cancer evaluation component for pentachlorophenol are clear, technically correct, and objectively presented.

Pentachlorophenol and By-Products of its Synthesis Disposition and Mechanisms

- Comment on whether the mechanistic data (Section 5: Mechanistic Data and Other Relevant Effects) are relevant for identifying and evaluating the potential mechanisms of action for the carcinogenic effects of pentachlorophenol.
  - Provide any scientific criticisms of the NTP's interpretation and application of the genotoxicity data (Section 5.1: Genetic and related effects) from the cited studies for assessing effects of pentachlorophenol.
  - Provide any scientific criticisms of the NTP's interpretation and application of the mechanistic data (Section 5.2: Mechanistic considerations) for assessing effects of pentachlorophenol.
  - Identify any information that should be added or deleted.

Draft RoC monograph on pentachlorophenol and by-products of its synthesis: Overall Cancer Evaluation

Evidence supporting that ‘pentachlorophenol and by-products of its synthesis’ is known to be a human carcinogen

- Studies in humans demonstrate a causal relationship between exposure to pentachlorophenol and by-products of its synthesis and non-Hodgkin lymphoma (NHL).
- Data support biological plausibility for a multisite carcinogen
  - Multiple cancer sites in studies of rats and mice with chronic dietary exposure
  - Mechanistic data demonstrating biological plausibility in humans
- Little is known about mechanisms of NHL in humans, but there are PCP exposure data suggesting overlap of mechanisms and associations that occur with NHL: immunosuppression and DNA damage (strand breaks), chromosome breakage, and inhibition of apoptosis.

Pentachlorophenol and By-Products of its Synthesis: Overall Cancer Evaluation

Preliminary listing recommendation

'Pentachlorophenol and by-products of its synthesis' is known to be a human carcinogen based on sufficient evidence from studies in humans demonstrating a causal relationship between exposure to pentachlorophenol and non-Hodgkin lymphoma. This conclusion is supported by sufficient evidence in experimental animals, and supporting mechanistic evidence.

Criteria: Page *v* of the Draft RoC Monograph on Pentachlorophenol and By-products of its Synthesis

Pentachlorophenol and By-products of its Synthesis: Overall Cancer Evaluation

Questions or Clarifications?

Overall Cancer Evaluation

- Comment on the overall cancer evaluation (Section 6: Overall Cancer Evaluation - Synthesis of Animal, Human, and Mechanistic Data) and whether the available metabolic, genotoxicity, and mechanistic data provide support for the relevance of the cancer studies in humans and experimental animals to human carcinogenicity.
  - Provide any scientific criticism of the NTP’s overall assessment and integration of the human cancer, experimental animal, and mechanistic data.

Draft RoC monograph on pentachlorophenol and by-products of its synthesis: Substance profile

Draft Substance Profile

- Contains NTP's preliminary recommendation of the listing status of the substance.
- Summarizes the scientific information that is key to reaching a recommendation.
- Provides information on properties, use, production and exposure.
- Provides information on existing federal regulations and guidelines.

Pentachlorophenol and By-Products of its Synthesis: Draft Substance Profile

Questions or Clarifications?

Draft Substance Profile

- Comment on whether the information on use, production, and human exposure for pentachlorophenol is clear and technically accurate.

- Comment on whether the information presented regarding cancer studies in humans is clear, technically correct, and objectively stated.
  - Comment on whether the substance profile highlights the information from the cancer studies in humans that are considered key to reaching the listing recommendation.

Draft Substance Profile

- Comment on whether the information presented regarding cancer studies in experimental animals is clear, technically correct, and objectively stated.
  - Comment on whether the substance profile highlights the key information from the cancer studies in experimental animals that supports the listing recommendation.

- Comment on whether the information presented regarding studies on mechanisms of carcinogenicity and other relevant data is clear, technically correct, and objectively stated.
  - Comment on whether the substance profile highlights the studies on mechanisms of carcinogenicity and other relevant data that are key to providing support for the carcinogenicity of pentachlorophenol in humans.

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Cancer studies in experimental animals

Strain (M & F)	Substance	Experimental design	Exposure period/ study duration	Reference
Rat: Diet				
F344/N	99% pure PCP	Carcinogenicity	2 yr/2 yr	Chhabra. 1999, NTP 1999
F344/N	99% pure PCP	Carcinogenicity	1 yr/2 yr	Chhabra 1999, NTP 1999
Sprague-Dawley	Dowicide EC-7	Carcinogenicity & reproductive	M: 22 mo/22 mo F: 24 mo/24 mo	Schwetz 1978
MRC-Wistar	Technical grade PCP	Co-carcinogen	94 wk/94 wk	Mirvish 1991
Mouse: Diet				
$B6C3F_1$	Technical grade PCP	Carcinogenicity	2 yr/2 yr	McConnell 1991, NTP 1989
$B6C3F_1$	Dowicide EC-7	Carcinogenicity	2 yr/2 yr	McConnell 1991, NTP 1989
$(C57BL/6xC3H/Anf)F_1$	Dowicide-7	Carcinogenicity	18 mo/18 mo	Innes 1969
$(C57BL/6xAKR)F_1$	Dowicide-7	Carcinogenicity	18 mo/18 mo	Innes 1969
CD-1 (F only)	99% pure PCP	Mechanism	12 mo/16 mo	Boberg 1983
CD-1 (F only)	99% pure PCP	Mechanism	10 mo/17 mo	Delclos 1986
C57BL/6-Trp53(+/-)tm1Dol	99% pure PCP	Short-term KO Carcinogenicity	26 wk/26 wk	Spalding 2000
Mouse: Dermal				
Tg.AC	99% pure PCP	Short-term Transgenic Carcinogenicity	20 wk/20wk	Spalding 2000