IARC MONOGRAPHS

SOME ORGANOPHOSPHATE INSECTICIDES AND HERBICIDES

VOLUME 112

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 3–10 March 2015

LYON, FRANCE - 2017

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

PARATHION

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 56-38-2

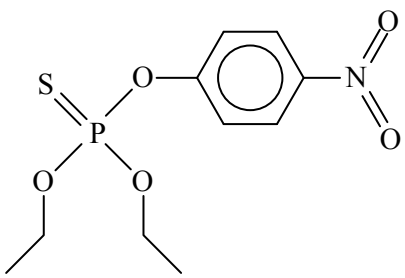
Chem. Abstr. Serv. Name: O,O-diethyl *O*-(4-nitrophenyl) phosphorothioate

Preferred IUPAC Name: O,O-diethyl *O*-(4-nitrophenyl) phosphorothioate

Synonyms: ethyl parathion; parathion-ethyl; thiophos

Selected Trade Names: Products containing parathion have been sold worldwide under several trade names, including Alkron; Alleron; Bladan; Bladan F; Corothion; Ethlon; Folidol; Fosfermo; Orthophos; Panthion; Paradust; Paraphos; Thiophos (IARC, 1983)

1.1.2 Structural and molecular formulae, and relative molecular mass



From NIST (2011)

Molecular formula: $C_{10}H_{14}NO_5PS$

Relative molecular mass: 291.26

Additional chemical structure information is available in the PubChem Compound database (NCBI, 2015).

1.1.3 Chemical and physical properties of the pure substance

Description: Solid below 6.1 °C (43°F), otherwise pale-yellow to dark-brown liquid with a garlic-like or phenol-like odour (NCBI, 2015)

Solubility: Very slightly soluble in water (11 mg/L at 20 °C, 24 mg/L at 25 °C) (IARC, 1983; NCBI, 2015); soluble in chloroform (Weast, 1988); miscible with most organic solvents; slightly soluble in petroleum oils (IARC, 1983; NCBI, 2015)

Volatility: Vapour pressure, reported as 6.68×10^{-6} mm Hg (20 °C) (NCBI, 2015); little volatilization from moist and dry soil surfaces is expected

Stability: Hydrolyses very slowly in acidic media, more rapidly in alkaline media to diethylphosphorothioic acid and *para*-nitrophenol; slowly isomerizes on heating above 130 °C to the *O,S*-diethyl analogue (IARC, 1983); decomposes above 200 °C to produce toxic gases including carbon monoxide, nitrogen oxides, phosphorous oxides, and sulfur oxides (IPCS, 2004).

Reactivity: Readily reduced to *O,O*-diethyl *O*-*para*-aminophenyl phosphorothioate; oxidized with difficulty to diethyl *para*-nitrophenyl

phosphate (Metcalf, 1981); reacts with strong oxidants (IPCS, 2004); attacks some forms of plastic, rubber and coatings (IPCS, 2004).

Octanol/water partition coefficient (P): log K_{ow}, 3.83 (NCBI, 2015)

Henry's law: 2.98×10^{-7} atm m^3 $mole^{-1}$ at 25 °C (HSDB, 2016), little volatilization from water surfaces is expected

Conversion factor: Assuming normal temperature (25 °C) and pressure (101 kPa), 1 mg/m^3 = 11.9 ppm (EPA, 2000b).

1.1.4 Technical products and impurities

Technical parathion is reported to be 96–98.5% active ingredient and 15% inert ingredients (IARC, 1983; HSDB, 2016). Observed impurities include diethyl and triethyl thiophosphates; nitrophenetole; nitrophenol; and the dithio analogue of parathion (Warner, 1975; IARC, 1983).

1.2 Production and use

1.2.1 Production

(a) Manufacturing

Parathion was introduced in 1947 and first registered in the USA in 1948 (IARC, 1983; EPA, 2000a). Ethyl parathion was only the second phenyl organophosphate introduced into agriculture, and the first to be used commercially (Ware & Whitacre, 2004).

Formulations including dusts (0.5–2% active ingredient); emulsifiable concentrates (2–8% active ingredient); granules (10% active ingredient); aerosols (10% active ingredient), and wettable powders (15–25% active ingredient) have been produced (IPCS, 1992).

(b) Production volume

Data on production volumes for parathion are very limited; however, it was listed as a chemical with a high production volume (> 1000 tonnes/year) in 2004 (OECD, 2004). Parathion is reported to be manufactured by seven producers worldwide: four in China, and one each in El Salvador, Germany, and the USA (AgriBusiness Global Sourcing Network, 2015). In the 1970s, parathion was manufactured in the USA by several companies, with an estimated total production of about 6000 tonnes per year, but only one company was still producing parathion in the 1990s (IARC, 1983; EPA, 2000a). Past production has also been reported in India in 1980–1981 at 1.2 tonnes, and around that same period annual production in western Europe was estimated to be in the range of 2000–5000 tonnes (IARC, 1983).

1.2.2 Uses

(a) Agriculture

Parathion is a broad spectrum, non-systemic, insecticide and miticide with contact, stomach, and some respiratory action (IPCS, 1992; EPA, 2000a). It has been used as a treatment for soil and foliage pre-harvest, and to control sucking and chewing insects, mites, and soil insects on a large variety of orchard, row, and field crops, including cereals, fruit, vines, vegetables, ornamentals, and cotton, both outdoors and in greenhouses (EPA, 2000a; IPCS, 1992; FAO/UNEP, 2005). When last used in the USA, parathion was restricted to nine crops: alfalfa, barley, rapeseed, corn, cotton, sorghum, soybean, sunflower, and wheat (EPA, 2000a).

(b) Regulation

Due to increasing concerns regarding hazards to wildlife and human health, the use of parathion as a pesticide has been banned, de-authorized or phased out by several counties including: Angola, Australia, Belize (1985), Bulgaria, China, Colombia (1991, except for on cotton using aerial equipment), Ecuador, El Salvador, Guatemala, Hungary, India (1974), Indonesia, Ireland, Japan (1955), Kuwait (1980), Malaysia, New Zealand (1987), Philippines, Portugal (1994), Russian

Table 1.1 Methods of analysis for parathion

Sample matrix	Analytical method	Limit of detection	Reference
Air	GC/FPD (phosphorus mode)	0.4 µg/m³	NIOSH (1994)
Water	GC/MS	0.15 µg/L	Munch et al. (2012)
Urine	Isotope dilution GC-MS/MS	9 µg/L (as 4-nitrophenol)	Fenske et al. (2002)
		0.2 µg/L (DEP) 0.1 µg/L (DETP)	Bravo et al. (2004)
Fruits and vegetables	GC/MS	0.03 mg/kg	Fillion et al. (2000)
Solids (soils, sediments, sludges)	GC/FPD (phosphorus mode)	NR	EPA (2007)
Dust	GC/MS (selected ion monitoring mode)	0.013-0.052 µg/g	Fenske et al. (2002)

DEP, diethylphosphate; DETP, diethylthiophosphate; FPD, flame photometric detector; GC, gas chromatography; MS, mass spectrometry

Federation, Sri Lanka (1984), Sweden (1971), the United Republic of Tanzania (1986), Thailand (1988), Turkey, United Kingdom, and the USA (2003) (IPCS, 1992; FAO, 1997; EPA, 2000a). In the European Community, all authorizations for plant protection products containing parathion were withdrawn by 2002; previously all formulations except capsule suspensions were included in Annex III of the Rotterdam Convention on international trade of hazardous chemicals (FAO/UNEP, 2005). In the USA, use sites and practices were restricted in 1991 to mitigate risk to workers; use was restricted to aerial equipment application of emulsifiable concentrates to nine specified crops, noted above, and all uses of parathion were terminated in 2003 (EPA, 2000a).

Limits for occupational exposure to parathion in air of 0.05–0.1 mg/m³ have been established in several countries (IFA, 2015). An acceptable daily intake of 0–0.005 mg/kg body weight (bw) from residues in food was established in 1967 (IPCS, 1992).

1.3 Measurement and analysis

Parathion is typically measured using "multi-residue" analytical techniques developed for the simultaneous measurement of a large number of organophosphate pesticides that might be present in a sample. Parathion can be measured in air, water, soil, dust, fruits and vegetables, and urine and faeces. The alkyl phosphate metabolites of parathion, diethylphosphate (DEP) and diethylthiophosphate (DETP), plus *para*-nitrophenol (also common to methyl-parathion) can be measured in urine. Representative chemical analysis methods for parathion and its metabolites are listed in Table 1.1.

In water and soil, most parathion degrades over several weeks but a small residual presence may remain in the soil for several months (HSDB, 2016).

1.4 Occurrence and exposure

1.4.1 Exposure

(a) Occupational exposure

The majority of exposure to workers is estimated to be via the dermal route (e.g. Cohen et al., 1979). Parathion poisoning has been reported in workers who had dermal contact with the foliage of treated fruit trees and vines (Quinby & Lemmon, 1958).

In the 1960s, dermal measurements of parathion during a range of different agricultural tasks were between 2.4 and 77.7 mg/hour, and respiratory levels were between 0.02 and 0.19 mg/hour (Wolfe et al., 1967). Exposure may vary considerably for a single task. For example, when spraying fruit trees, dermal exposure to parathion varied by up to 200-fold depending

on the environmental conditions (particularly wind), the method of application (upward spraying equipment gave more exposure than downward spraying equipment), rate of application, and operator technique (Wolfe et al., 1967).

A study of 57 workers in a plant manufacturing powdered parathion found mean dermal exposures of 67.3 mg/hour and mean respiratory exposures of 0.62 mg/hour (Wolfe et al., 1978). The highest exposures were found in those undertaking bagging tasks.

Farm workers hand-harvesting onions (n = 64) had a geometric mean dermal exposure of 0.84 µg/hour for the first day, and 0.36 µg/hour for the second day (Munn et al., 1985). There was no difference in exposure by age or sex of the worker.

A study of ambient parathion concentrations in aeroplane cockpits during aerial spraying have shown very high peak levels (up to 440 µg/mL) over short intervals (between 11 and 21 minutes). Spraying pilots and ground crews also showed reduced whole blood cholinesterase activity (Richter et al., 1980).

A study of 14 workers in cotton fields sprayed with parathion in the USA reported a small decline in plasma and erythrocyte cholinesterase activity in a group that entered a field 24 hours after treatment, and a larger decline among a group exposed 48 hours after treatment and following a light rain (Ware et al., 1974).

(b) Community exposures

The general population can be exposed to parathion from drinking-water, residues on food, spray drift from nearby farms, and para-occupational sources (EPA, 2000b).

(i) Drinking-water

Parathion has been rarely detected in groundwater or surface water in the USA (Gilliom et al., 2006). The concentration of ethyl parathion was reported as 0 ppb for all of the 410 measurements in surface water recorded in the Surface Water Protection Program Database of the California Department of Pesticide Regulation (2015). Data from other countries were not available to the Working Group.

(ii) Residues on food

Parathion residues are rarely detected on food in recent data from the USA, Canada, and the European Union (Rawn et al., 2004; EFSA, 2011; FDA, 2015). Parathion was not detected in 226 samples of 7 types of vegetables from Hebei Province, China (Li et al., 2014). In a study in Shaanxi, China, parathion was not detectable in 60 samples of cereals, or 60 samples of fruit; however, it was detected in 2 out of 80 samples of vegetables, and the mean concentrations of parathion exceeded the national maximum residue limit (Bai et al., 2006). Parathion residues were detected in 10–16% of sampled tomatoes, eggplant, and peppers purchased at a market in Ghana, with concentrations ranging from 0.061 to 0.089 mg/kg (Darko & Akoto, 2008).

(iii) House dust

In Washington state, USA, dust in the houses of 12 farmworkers and 49 pesticide applicators was tested for ethyl parathion (Fenske et al., 2002). It was found in 48% of houses, more often in the houses of applicators than in those of general farm workers; the arithmetic mean concentration was 0.06 µg/g with a range of 0 to 0.95 µg/g. Another study of 48 agricultural families and 11 reference families in Washington state detected parathion in dust in homes of 69% of agricultural families and 27% of reference families, with mean levels of 0.365 µg/g and 0.076 µg/g, respectively (Simcox et al., 1995). Among the agricultural workers, levels were higher in farmers and applicators than farmworkers.

1.4.2 Exposure assessment and biological markers

Exposure assessment methods in epidemiological studies on parathion and cancer are discussed in Section 1.4.2 and Section 2.1.2 of the *Monograph* on Malathion, in the present volume.

There are no biomarkers that are specific for parathion. Urinary and blood measures of breakdown products of parathion and suppression of acetylcholinesterase activity are only useful to measure parathion when exposure to any other organophosphate pesticide can be definitively ruled out.

2. Cancer in Humans

2.1 Introduction

In previous *IARC Monographs* (IARC, 1983, 1987), parathion was evaluated as *Group 3, unclassifiable as to carcinogenicity in humans*, as there was no evidence to evaluate direct exposure in humans. Although relevant reports have since been published, there is still relatively little epidemiological literature on whether there is an association between cancer and exposure to parathion. In contrast, the general class of organophosphate insecticides has been more heavily investigated, and while parathion is a member of this class, other members are used in greater frequency and amounts (e.g. diazinon, malathion, chlorpyrifos, etc.), which has resulted in their more frequent examination in published reports. The organophosphate insecticides are part of the grouping of "non-arsenical insecticides," which in 1991 were classified as *Group 2A, probably carcinogenic to humans* (IARC, 1991).

A general discussion of the epidemiological studies on agents considered in the present volume (Volume 112) of the *IARC Monographs* is presented in Section 2.2 of the *Monograph* on Malathion. The scope of the available epidemiological studies is discussed in Section 2.1 of the *Monograph* on Malathion, and includes a consideration of chance, bias and confounding, and exposure assessment.

2.2 Cohort studies

2.2.1 Agricultural Health Study

Epidemiological evidence regarding parathion derived from cohort studies (Table 2.1) has been largely from the Agricultural Health Study (AHS). The AHS is a prospective cohort of licensed pesticide applicators enrolled in 1993–1997 in Iowa and North Carolina, USA (Alavanja et al., 1996; see the *Monograph* on Malathion, Section 2.2, for a detailed description of this study).

Engel et al. (2005) examined whether exposure to pesticides was associated with incidence of cancer of the breast among farmers' wives in the AHS cohort, as this cancer occurred frequently enough to be studied after a minimum of only 3 years of follow-up. The study included 30 454 women with no history of cancer of the breast before cohort enrolment in 1993–1997. Parathion was one of 24 specific pesticides for which results were reported. Personal use of parathion was reported for fewer than three women, which was too few for a relative risk estimate to be calculated. The relative risk of cancer of the breast among women whose husbands used parathion was not significant overall, but statistically significant associations were detected with stratification by state or family history of breast cancer (and there was also an elevated but not significant relative risk (RR) for postmenopausal breast cancer). Husband's use of parathion was reported for 18 (13%) cases and 1385 (11%) controls, yielding a relative risk of 1.3 (95% CI, 0.8–2.1). Stratified analyses suggested that the association with husband's parathion use was stronger in Iowa (RR, 2.0; 95% CI, 1.0–4.1) than in North Carolina (RR, 0.9; 95% CI, 0.5–1.8); and may be higher with postmenopausal (RR, 1.4; 95% CI, 0.8–2.5)

Table 2.1 Cohort studies of cancer and exposure to parathion

Study name, reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Florida Pest Control Worker Study Pesatori et al. (1994) Florida, USA Enrolment, 1965–66; follow-up until 1982 Nested case–control study	Cases: 65 (response rate, 83%); identified from the Florida pest control workers cohort Controls: 294 (122 deceased, 172 living) (response rates: deceased controls, 80%, living controls, 75%) Exposure assessment method: questionnaire	Lung	Ever vs never (living controls)	6	3.2 (0.5–20.7)	Age, smoking
AHS Engel et al. (2005) IA and NC, USA Enrolment, 1993–1997; follow-up to 2000	30 454 wives of male licensed pesticide applicators, with no history of breast cancer at enrolment Exposure assessment method: questionnaire	Breast	Husband's use (indirect exposure)	18	1.3 (0.8–2.1)	Age, race (white/other), state of residence
			By state – IA	8	2.0 (1.0–4.1)	
			By state – NC	10	0.9 (0.5–1.8)	
			Premenopausal	3	0.9 (0.3–3.0)	
			Postmenopausal	13	1.4 (0.8–2.5)	
			No family history of breast cancer	11	0.9 (0.5–1.8)	
			Family history of breast cancer	7	4.2 (1.6–10.6)	
AHS Lee et al. (2007) IA and NC, USA Enrolment, 1993–1997; follow-up to 2002	56 813 licensed pesticide applicators with no prior history of colorectal cancer (97% males) Exposure assessment method: questionnaire	Colorectum	Ever use	46	0.9 (0.6–1.3)	Age, smoking, state, total days of pesticide use
		Colon	Ever use	31	0.9 (0.6–1.5)	
		Rectum	Ever use	15	0.9 (0.5–1.7)	
AHS Dennis et al. (2010) IA and NC, USA 1993–2005	25 291 licensed pesticide applicators (mostly farmers) (24 704 in analysis) Exposure assessment method: questionnaire	Melanoma	Ever use	21	1.9 (1.2–3.0)	Age, sex, tendency to burn, red hair, sun exposure duration, BMI Prevalence of parathion use in whole cohort = 11% (7% for non-cases; 15% for cases)
			Not exposed to lead arsenate	13	1.5 (0.8–2.7)	
			Exposed to lead arsenate	8	7.3 (1.5–34.6)	
			Low exposure (< 56 days)	10	1.6 (0.8–3.1)	
			High exposure (≥ 56 days)	11	2.4 (1.3–4.4)	
			Trend-test *P* value: 0.003			

Table 2.1 (continued)

Study name, reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
AHS Alavanja et al. (2014) IA and NC, USA Enrolment, 1993–1997; follow up 2010 in NC, and 2011 in IA	54 306 licensed pesticide applicators (523 incident cases of NHL) with no prevalent cancer at baseline, not living outside the catchment area of IA and NC cancer registries, and with complete data on potential confounders Exposure assessment method: questionnaire	NHL (including multiple myeloma)	Ever used	69	1.1 (0.8–1.4)	Age, state, race (white/black), total days of herbicide use
			Low (LED, ≤ 8.75)	9	1.0 (0.5–2.0)	
			Medium (LED, > 8.75–24.5)	6	1.4 (0.6–3.2)	
			High (LED, > 24.5)	6	0.8 (0.3–1.8)	
			Trend-test *P* value: 0.64			
		NHL (including multiple myeloma)	IW-LED			
			Low (≤ 8.75)	7	0.9 (0.4–2.0)	
			Medium (> 8.75–24.5)	8	1.4 (0.7–2.9)	
			High (> 24.5)	6	0.8 (0.4–1.9)	
			Trend-test *P* value: 0.74			
AHS Koutros et al. (2013) IA and NC, USA Enrolment, 1993–1997; follow-up to 2007	54 412 licensed private pesticide applicators (IA and NC) and 4916 licensed commercial applicators (IA); 1962 incident cases including 919 aggressive cancers Exposure assessment method: questionnaire	Prostate, total cancers	IW-LED:			Age, state, race, smoking, fruit servings, family history of prostate cancer, and physical activity A prior AHS publication already reported on diazinon and prostate cancer (Beane Freeman et al., 2004), but here 5 years additional follow-up were included
			Quartile 1 (low use)	25	1.21 (0.81–1.81)	
			Quartile 2	25	1.37 (0.92–2.05)	
			Quartile 3	25	1.21 (0.81–1.81)	
			Quartile 4 (high use)	24	0.85 (0.56–1.28)	
			Trend-test *P* value: 0.51			

Table 2.1 (continued)

Study name, reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
AHS Koutros et al. (2013) IA and NC, USA Enrolment, 1993–1997; follow-up to 2007 (cont.)		Prostate, aggressive cancers	Quartile 1 (low use)	12	1.96 (1.1–3.5)	
			Quartile 2	12	1.04 (0.58–1.86)	
			Quartile 3	12	1.5 (0.82–2.77)	
			Quartile 4 (high use)	11	0.98 (0.53–1.79)	
			Trend-test *P* value: 0.97			
		Prostate (no family history)	Quartile 1 (low use)	16	1.14 (0.69–1.87)	
			Quartile 2	18	1.36 (0.85–2.19)	
			Quartile 3	16	1.08 (0.66–1.79)	
			Quartile 4 (high use)	20	0.99 (0.63–1.55)	
			Trend-test *P* value: 0.98			
		Prostate (with family history)	Quartile 1 (low use)	5	1.32 (0.54–3.23)	
			Quartile 2	5	1.54 (0.63–3.8)	
			Quartile 3	6	1.58 (0.65–3.84)	
			Quartile 4 (high use)	3	–	
			Trend-test *P* value: 0.88			
			GC rs7041			Age, state
			Low exposure – CC	12	2.58 (1.07–6.25)	
			High exposure – CC	10	3.09 (1.1–8.68)	
			Trend-test *P* value: $P < 0.01$			

Table 2.1 (continued)

Study name, reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
AHS Koutros et al. (2013) IA and NC, USA Enrolment, 1993–1997; follow-up to 2007 (cont.)		Prostate	Never vs IW-LED			Age, state
			Ever used	102	1.02 (0.78–1.33)	
			Low level	30	1.28 (0.79–2.06)	
			High level	22	0.9 (0.53–1.54)	
			Trend-test *P* value: 0.91			
		Prostate	*RXRB* rs1547387			Age, state
			Low exposure – CC	22	1.12 (0.65–1.94)	
			High exposure – CC	12	0.54 (0.28–1.04)	
			Low exposure – CG + GG	8	1.82 (0.68–4.89)	
			High exposure – CG + GG	10	4.27 (1.32–13.78)	
			Trend test *P* value, < 0.01			
		Prostate	*GC* rs222040			Age, state
			Low exposure – AA	11	2.14 (0.89–5.12)	
			High exposure – AA	11	3.39 (1.23–9.36)	

AHS, Agricultural Health Study; CI, confidence interval; *GC*, Group specific Component gene; IA, Iowa; IW-LED, intensity-weighted lifetime days of use; NC, North Carolina; NR, not reported; *RXRB*, Retinoid-X-Receptor-β gene

than premenopausal (RR, 0.9; 95% CI, 0.3–3.0) breast cancer. The effect varied by family history (*P* value for interaction = 0.04): among women with a family history of breast cancer there was a relative risk of 4.2 (95% CI, 1.6–10.6; 7 exposed cases; exposure prevalence, 19%) associated with exposure to parathion, while among those who did not have a family history, the relative risk was 0.9 (95% CI, 0.5–1.8; 11 (9%) exposed cases). [The strengths of this study included its large sample size, comprehensive exposure assessment, extent of potential confounder control, and exploration of potential interactions, such as by family history. To date, this is the only study to have reported on whether parathion is associated with cancer in women.]

Cancer of the colorectum was studied by Lee et al. (2007) in the AHS, with a total of 305 incident cases of cancer of the colorectum (colon, 212; rectum, 93) diagnosed during the study period, 1993–2002. Among the 50 pesticides examined, use of parathion was reported in 46 (20%) cases of cancer of the colorectum, with a relative risk of 0.9 (95% CI, 0.6–1.3); use of parathion varied very little according to whether the cancer was of the colon or rectum. Given that no association was seen for parathion in the ever versus never analysis, and that there were no a-priori hypotheses or previous results related to parathion, there was no further analysis of exposure–response relationships. [The Working Group noted that the large sample size provided a relatively precise null result, and that among the many potential confounders considered, the final models included an indicator of exposure to other pesticides.]

The incidence of cutaneous melanoma was studied within the AHS by Dennis et al. (2010), with an average length of follow-up of 10.3 years until 2005. This study focused on the AHS subset for which data on arsenical pesticides were available, that is, the 24 704 pesticide applicators (43% of the full AHS cohort) who completed the more detailed take-home questionnaire in addition to the baseline questionnaire. Of the 50 specific pesticides assessed, 4 were found to be associated with risk of melanoma (parathion, benomyl, carbaryl, maneb/mancozeb), and these 4 were further analysed to assess whether results varied with use of lead arsenate. Dennis et al. also assessed whether the observed relationship between exposure to parathion and risk of melanoma was modified by exposure to arsenic compounds; previous reports had suggested that arsenic exposure may be related to melanoma (Beane Freeman et al., 2004), that arsenic may interact with certain pesticides and sun exposure in causing skin lesions (Chen et al., 2006), and that sunscreen may increase absorption of parathion (Brand et al., 2003). A total of 150 incident cases of cutaneous melanoma were detected, and use of parathion was reported by 11% of the whole cohort, with 21 (15%) exposed cases. The odds ratio for ever versus never use of parathion was 1.9 (95% CI, 1.2–3.0), and a monotonic trend was found with increasing level of exposure: the odds ratio was 1.6 (95% CI, 0.8–3.1) for < 56 exposure-days, compared with 2.4 (95% CI, 1.3–4.4) for ≥ 56 lifetime exposure-days (*P* value for trend = 0.003). Both these analyses were based on models that adjusted for major potential confounders, including age, sex, burn tendency, red hair, duration of sun exposure, and body mass index. There was no effect modification of the association with pesticides by sun exposure [stated by authors, data not presented]. A possible statistical interaction was detected between use of parathion and exposure to lead arsenate (*P* value for interaction = 0.065), since among workers who had used lead arsenate there was a significant association (OR, 7.3; 95% CI, 1.5–34.6; 8 exposed cases), compared with those who did not use lead arsenate (OR, 1.5; 95% CI, 0.8–2.7; 13 exposed cases). [There was potentially plausible effect modification, with risk increased among those who also applied lead arsenate. Although Dennis et al. (2010) controlled for the potential effects of established risk factors for melanoma,

sun exposure and duration of pesticide use are likely to be correlated so there was potential for residual confounding in the effect estimates for each pesticide. Also, results arising from the testing of multiple exposures and interactions must be interpreted with caution; however, the combination of main effect, gradient of effect, and potentially plausible effect modification provided support for the hypothesis that exposure to parathion and other agricultural chemicals may be an additional source of risk beyond established risk factors for melanoma (e.g. host factors, susceptibility, and sun exposure).]

Cancer of the prostate was assessed in the AHS by Koutros et al. (2013), with follow-up to 2007, which resulted in 1962 incident cases among the full cohort of 54 412 pesticide applicators. For persons who did not respond to the questionnaire regarding parathion use, values were imputed. [The Working Group noted that Heltshe et al. (2012) demonstrated there was a very high level of agreement between observed and imputed values, in part due to the rarity of exposure to parathion.] The relationship between exposure and incidence of cancer of the prostate was assessed for 48 pesticides, plus stratified analyses assessed whether associations varied according to the aggressiveness of the tumour, or family history of prostate cancer. Aggressive cancer of the prostate was defined as having one or more of the following features: distant stage, poorly differentiated grade, Gleason score ≥ 7, or fatality. Due to updates in grade classification by pathologists, Gleason scores for cases diagnosed before 2003 were re-abstracted and analyses were repeated for alternative definitions of aggressiveness. Results for parathion demonstrated that in general there was neither a statistically significant increase in risk, nor a trend for all cancers of the prostate (*P* value for trend = 0.51) or aggressive cancers of the prostate (*P* value for trend = 0.97); with the exception of a significantly increased risk of aggressive cancer of the prostate in the lowest quintile of parathion exposure (OR for Q1, 1.96; 95% CI, 1.1–3.5). Stratification by family history of cancer of the prostate did not result in statistically significant associations or trends. Although the odds ratio estimates for all quartiles of exposure were > 1.0 for men with a family history of cancer of the prostate, the estimates were imprecise due to small numbers (i.e. there were 6 or fewer exposed cases in each quartile). [The Working Group noted that this study included well-characterized exposures and outcomes, and a large sample size that enabled relative risk estimation while controlling for multiple potential confounders, and stratifying for features such as tumour traits, resulting in the detection of an association for aggressive prostate cancers, but not for all prostate cancers.]

A case–control study on cancer of the prostate, nested within the AHS, was reported by Karami et al. (2013); the unique contribution of this study was the exploration of whether certain pesticides may be linked to cancer of the prostate via an interaction with vitamin D-related genetic variants. The motivation for this study was stated to be that anti-carcinogenic effects of vitamin D and its metabolites (e.g. by stimulating cell differentiation, inhibiting cell proliferation or inducing apoptosis) may be reduced by certain pesticides. Karami et al. (2013) compared 776 cases of cancer of the prostate and 1444 controls, who were white, male, pesticide applicators. Interactions were evaluated between 41 pesticides and 152 single-nucleotide polymorphisms (SNPs) in nine genes involved in vitamin D pathways, after adjusting for false discovery rate, to account for multiple comparisons. Parathion use was not associated with cancer of the prostate (OR for ever use, 1.02; 95% CI, 0.78–1.33; *P* value for trend = 0.91). However, statistical interactions were detected between use of parathion and two vitamin D-related genes: the strongest interaction observed was between the *RXRB* gene variant rs1547387 and parathion [(*RXRB* is the Retinoid-X-Receptor-beta gene that is involved in binding vitamin D to vitamin D receptors).

No previously published study has evaluated the association between this specific SNP and cancer.] Significant interactions were also observed between parathion and the *GC* gene (Group specific Component, which is a binding protein that carries vitamin D in blood) variants rs7041 and rs222040. [Ahn et al. (2009) previously showed that the presence of the variant form of the *GC* gene was associated with reduced levels of circulating vitamin D (25-OH-D) in the Prostate, Lung, Colon and Ovary (PLCO) Screening Trial.] The exposure–response pattern among participants with increasing use of parathion and the variant form (G) of the rs1547387 SNP of the *RXRB* gene and the homozygote CC genotype for the *GC* gene in the rs7041 SNP (which alters circulating vitamin D levels) was noteworthy when compared with unexposed participants. [The Working Group noted that this result was not independent from that of the previous study of prostate cancer within the AHS, and confirmed that overall there was no association between exposure to parathion and prostate cancer. However, the contribution of this study was the analysis of potential modification of pesticide effects by genetic variation involving the vitamin D pathway. This study was large enough to allow examination and detection of trends with exposure level in subsets defined by the genetic variants.]

Alavanja et al. (2014) investigated whether exposure to pesticides influenced the risk of non-Hodgkin lymphoma (NHL) and its subtypes in the AHS. Ever having used parathion was not associated with NHL overall (RR, 1.1; 95% CI, 0.8–1.4) or by subtype (small lymphocytic lymphoma/chronic lymphocytic leukaemia/mantle cell lymphoma; diffuse large B-cell lymphoma; follicular B-cell lymphoma; multiple myeloma), and there was no evidence of heterogeneity across subtypes (e.g. relative risk estimates were 1.0 or 1.1 for each subtype). There was no monotonic trend with categories of total days of lifetime use (*P* value for trend = 0.64) or intensity-weighted lifetime days of use (*P* value for trend = 0.74). [The strengths of this analysis were that the comprehensive data permitted controls for multiple confounders, including indicators of total use of other pesticides, and that the large sample size enabled separate analyses of the heterogeneous subtypes of NHL.]

2.2.2 Other cohort studies

A nested case–control study derived from a previous occupational cohort study was reported by Pesatori et al. (1994) (Table 2.1). This was based on a cohort of Florida pest control workers whose licensing records were linked with mortality files (e.g. national death index, death certificates, social security mortality files) (see the *Monograph* on Malathion, Section 2.2, for a detailed description of this study). Parathion use was reported for 2 (3%) cases, 0 deceased controls, and 6 (3%) of living controls, which for the latter resulted in an odds ratio of 3.2 (95% CI, 0.5–20.7) with adjustment for age and smoking [The Working Group noted that the report stated that adjustments for diet, other occupations and other factors did not alter risk estimates. This study was limited by its small size (with 65 deceased cases), and the potential for exposure misclassification by collecting pesticide exposure by interviewing next of kin. The wide confidence interval for the odds ratio demonstrated the imprecision of this estimate due to the modest size of the cohort and the rarity of parathion use.]

2.3 Case–control studies

2.3.1 Case–control studies on lympho-haematopoietic cancers

A single case–control study reported on whether exposure to parathion was associated with risk of lymphoma (Table 2.2). Waddell et al. (2001) pooled data from three case–control studies of NHL among white men in the USA

Table 2.2 Case–control study of lympho-haematopoietic cancers and exposure to parathion

Reference, location follow-up/enrolment period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Waddell et al. (2001) Iowa, Minnesota, Kansas, Nebraska, USA 1979–1986	Cases: 748 (response rate, 83%) from tumour registries, clinical groups, and hospitals Controls: 2236 (response rate, 86%) living cases from health service administration records; deceased cases from mortality records Exposure assessment method: questionnaire; Iowa & Minnesota: see Cantor et al. (1992); Kansas: telephone interview, days/year of pesticide use and years of use were asked about herbicides and insecticides overall, not by specific pesticide; subjects were asked to volunteer the pesticides they used; Nebraska: telephone interview days per year of use and years of use were asked for each pesticide used; asked about a predetermined list of about 90 pesticides	NHL	Ever use	5	2.9 (0.9–9.7)	Age, state, proxy/direct respondent	Studies in midwest USA (pooled)

NHL, non-Hodgkin lymphoma

(Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) to evaluate organophosphate pesticides, including parathion, as used by farmers. The three studies were population-based and yielded 748 cases of NHL and 2236 controls (see the *Monograph* on Malathion, Section 2.2, for a detailed description of this study). Detailed subset analyses (e.g. by histological type, state) were done for five pesticides, but this could not be done for parathion due to the rarity with which it was used. Comparing farmers using parathion to non-farmers yielded an odds ratio of 2.9 (95% CI, 0.9–9.7; 5 exposed cases; 8 exposed controls) adjusted for age, state and respondent type (direct versus proxy). [The strengths of this report included the large sample size, which enabled assessment of infrequent exposure to parathion; however, the study was not sufficiently large to detect a gradient of effect. While several potential confounders were considered, the result must be interpreted with caution since the effect of parathion could be confounded by other pesticides that were not controlled for in the analysis.]

2.3.2 Case–control studies on other cancers

Band et al. (2011) reported on a case–control study of cancer of the prostate, for which all male cancer patients identified in the population-based cancer registry for British Columbia, Canada, from 1983 to 1990 were invited to complete a self-administered occupational history and questionnaire, and for whom a job-exposure matrix (JEM) was developed (see the *Monograph* on Malathion, Section 2.2, for a detailed description of this study). Results for 100 pesticides were presented in the report, and it was estimated that 30 (2%) cases and 63 (1%) controls had used parathion, for an odds ratio of 1.51 (95% CI, 0.94–2.41), after adjusting for alcohol, smoking, education, and type of respondent (proxy/direct). With exposure levels defined as above or below the median number of lifetime days on which parathion was used, compared with never users, the odds ratios for low and high use were 1.29 (95% CI, 0.66–2.50) and 1.82 (95% CI, 0.94–3.53), respectively, with a *P* value for the trend of 0.06. [While strengthened by the large number of cases, the results of this study should be interpreted with caution due to the many comparisons examined, the correlated nature of occupational exposures, and the potential misclassification that derives from using a JEM to estimate individual exposures to parathion.]

2.4 Meta-analyses

No data were available to the Working Group.

3. Cancer in Experimental Animals

Studies of carcinogenicity previously assessed by the Working Group (IARC, 1983), and leading to the previous evaluation of *inadequate evidence* in experimental animals for the carcinogenicity of parathion (IARC, 1987), were also included in the present *Monograph*.

3.1 Mouse

See Table 3.1

Oral administration

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 5 weeks) were fed diets containing parathion (purity, 99.5%; impurities unspecified) at a concentration of 80 or 160 ppm for 71 and 62 weeks, respectively (males), and for 80 weeks (females). Male mice were then observed for 18 and 28 weeks, respectively, while female mice were observed for 9 and 10 weeks, respectively. A matched control group of 10 males and 10 females was observed for 90 weeks. Since the numbers of mice in the matched control groups were small, pooled control groups of 140 males and 130 females were also used for statistical

Table 3.1 Studies of carcinogenicity with parathion in mice

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence (%) of tumours	Significance	Comments
B6C3F$_1$ (M, F) 89–90 wk NTP (1979)	Diets containing parathion (purity, 99.5%) at 0 ppm (matched control), 80 ppm, or 160 ppm, ad libitum, 7 days/wk: lower-dose males for 71 wk and then held untreated for an additional 18 wk; higher-dose males for 62 wk and then held untreated for an additional 28 wk; lower- and higher-dose females for 80 wk and then held untreated for an additional 9–10 wk 50 M and 50 F/treated group Since the numbers of mice in the matched-control groups were small, pooled-control groups also were used for statistical comparisons 10 M and 10 F/matched –control group 140 M and 130 F/pooled-control group	No tumours occurred in either sex at incidences that were significantly higher in the dosed groups than in the corresponding matched or pooled control groups	NS	Short duration of treatment, and small number of matched controls Pooled controls: matched controls from study on parathion were combined with matched controls from long-term studies on azinphosmethyl, chlordane, dieldrin, dimethoate, heptachlor, lindane, malathion, phosphamidon, photodieldrin, and tetrachlorvinphos
B6C3F$_1$ (M, F) 18 mo EPA (1991a)	Diets containing parathion (purity, 96.7%) at 0 (control), 60, 100, or 140 ppm for 18 mo 50 M and 50 F/group [age, NR]	*Males* Bronchiolo-alveolar adenoma[a]: 5/50 (10%), 13/50 (26%)*, 6/50 (12%), 4/50 (8%) Bronchiolo-alveolar carcinoma[b]: 0/50, 1/50 (2%), 0/50, 0/50 Bronchiolo-alveolar adenoma or carcinoma (combined): 5/50 (10%), 14/50 (28%)**, 6/50 (12%), 4/50 (8%) *Females* Malignant lymphoma[c]: 0/50, 5/50 (10%)***, 3/50 (6%), 2/50 (4%) Histiocytic sarcoma[d]: 0/50, 1/50 (2%), 0/50, 2/50 (4%)	*P = 0.033 **P = 0.020 ***P = 0.028	Lowest-dose mice were incorrectly dosed with parathion at 500 ppm on days 300–307. These mice were switched to control diet for 17 days to recover, and then returned to the correct dose level. Six males and two females at the lowest dose died within 14 days of the misdosing There was a dose-related decrease in body weight in males and females without treatment-related increase in mortality

[a] Historical controls at testing laboratory: 16/150 (11%); range, 10–12%
[b] Historical controls at testing laboratory: 10/150 (7%); range, 2–12%
[c] Historical controls at testing laboratory: 41/150 (27%); range, 24–32%
[d] Historical controls at testing laboratory: 0/150
F, female; M, male; mo, month; NR, not reported; NS, not significant; wk, week

comparisons. Matched controls from the study on parathion were combined with matched controls from other long-term studies performed at the same laboratory on azinphosmethyl, chlordane, dieldrin, dimethoate, heptachlor, lindane, malathion, phosphamidon, photodieldrin, and tetrachlorvinphos. By the end of the experiment (89 weeks), 80% of males at the highest dose, 92% of females at the highest dose, 92% of males and females at the lowest dose, 100% of matched-control males, and 80% of matched-control females were still alive. Full histopathology was performed. There was no significant increase in tumour incidence observed in any of the tissues examined compared with matched or pooled controls (NTP, 1979). [The Working Group noted the short duration of treatment and the small number of matched controls.]

A report by the United States Environmental Protection Agency (EPA, 1991a) provided information on a study in which groups of 50 male and 50 female B6C3F$_1$ mice [age not specified] were fed diets containing parathion (purity, 96.7%) at a concentration of 0 ppm, 60 ppm, 100 ppm, or 140 ppm, ad libitum, 7 days per week for 18 months. Mice at the lowest dose were mistakenly dosed with parathion at 500 ppm between days 300 and 307 of the study. These mice were switched to control diet for 17 days to recover and then returned to the proper dose level. Six males at the lowest dose and two females at the lowest dose died within 14 days of the misdosing. There was a dose-related decrease in body weight in males and females without treatment-induced increase in mortality. The only increases in tumour incidence that were statistically significant were observed in the groups at 60 ppm. The incidences were: 5/50 (10%, control), 13/50 (26%, $P = 0.033$), 6/50 (12%), 4/50 (8%) for bronchiolo-alveolar adenoma in males; 5/50 (10%, control), 14/50 (28%, $P = 0.020$), 6/50 (12%), 4/50 (8%) for bronchiolo-alveolar adenoma or carcinoma (combined) in males; and 0/50 (0%, control), 5/50 (10%, $P = 0.028$), 3/50 (6%), 2/50 (4.0%) for malignant lymphoma in females. At 60 ppm, the incidence of bronchiolo-alveolar adenoma in males (13/50; 26%) exceeded the upper bound of the range reported for historical controls at the testing laboratory (16/150; 11%; range, 10–12%); the incidence of bronchiolo-alveolar carcinoma in males (1/50; 2%) was within the range for historical controls (10/150; 7%; range, 2–12%); and the incidence of malignant lymphoma in females (5/50; 10%) was below the lower bound of the range for historical controls (41/150; 27%; range, 24–32%). [The Working Group noted that tumour incidences were significantly increased only in the group receiving the lowest dose (60 ppm), which had been misdosed.]

3.2 Rat

See Table 3.2

3.2.1 Oral administration

Hazleton & Holland (1950) reported two studies in albino rats [strain and age at start not reported; body weight, 60–70 g], fed diets containing parathion (purity, 95–97%; impurities unspecified) at different concentrations. Two groups of 20 male rats received parathion at a concentration of 10 or 25 ppm for 88 weeks. Two groups of male rats received parathion at a concentration of 50 (10 rats) or 100 ppm (8 rats) for 104 weeks. There were two control groups of 10 and 20 male rats, respectively. In addition, groups of 8–9 female rats received parathion at a concentration of 10 or 50 ppm for 64 weeks, and 6 females served as controls. Survival of males was 69% at 10 ppm, 87% at 25 ppm, and 60% in the first control group; 80% at 50 ppm, 62% at 100 ppm, and 70% in the second control group. Survival of females was 100% at 10 ppm, 62% at 50 ppm, and 67% in controls. Macroscopic examination of the rats, and microscopic examination of a limited number of tissues from males in the groups at 50 ppm and 100 ppm, did not reveal

Table 3.2 Studies of carcinogenicity with parathion in rats

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence (%) of tumours	Significance	Comments
Albino [strain, NR] (M, F) 64–104 wk Hazleton & Holland (1950)	Diets containing parathion (purity, 95–97%) at 0, 10, 25, 50, or 100 ppm for 64–104 wk 8–20 M and 6–9 F/group (age at start, NR)	Macroscopic examination of the rats and microscopic examination of a limited number of tissues from males at 50 ppm or 100 ppm (exposed for 104 wk) revealed no tumours	NS	Small number of tested rats, and small number of organs used for histopathological examination; limited reporting of the study
Albino [strain, NR] (M, F) ≤ 12 mo Barnes & Denz (1951)	Diets containing parathion (purity, 76.8%) in ethanol at 0, 10, 20 or 50 ppm, for 6 days/wk for 12 mo; or 75 or 100 ppm for 27 or 19 days, respectively, and these rats were observed for up to 12 mo 36 M and 36 F (age, 6 wk)/treated group 30 M and 30 F (age, 6 wk)/control group	No evidence of tumours, with the exception of one spindle cell sarcoma of the mediastinum in one rat at 20 ppm	NS	Short duration of exposure and observation periods, and small number of rats undergoing histopathological examination; limited reporting of the study

Table 3.2 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence (%) of tumours	Significance	Comments
Osborne-Mendel (M, F) ≤ 113 wk NTP (1979)	Diets containing parathion (purity, 99.5%), ad libitum, 7days/wk, at 0 ppm (M and F; matched controls); 32 ppm TWA (lowest-dose M – 40 ppm for 13 wk then lowered to 30 ppm for 67 wk); 63 ppm TWA (highest-dose M – 80 ppm for 13 wk then lowered to 60 ppm for 67 wk); 23 ppm TWA (lowest-dose F – 20 ppm for 13 wk, then increased to 30 ppm for 21 wk, and then lowered to 20 ppm for 46 wk); or 45 ppm TWA (highest-dose F – 40 ppm for 13 wk, then increased to 60 ppm for 21 wk, and then lowered to 40 ppm for 46 wk). The rats were held untreated until experimental wk 112–113 Since the numbers of rats in the matched control groups were small, pooled control groups also were used for statistical comparisons 50 M and 50 F/treated group 10 M, 10 F/matched-control group 90 M, 90 F/pooled-control group	*Males* Adrenal cortical adenoma: 0/9 (matched control), 2/80 (3%, pooled control), 5/49 (10%), 9/46 (20%) Adrenal cortical adenoma or carcinoma (combined): 0/9 (matched control), 3/80 (4%, pooled control), 7/49 (14%), 11/46 (24%) Thyroid follicular-cell adenoma: 3/10 (30%, matched control), 5/76 (7%, pooled control), 2/46 (4%), 8/43 (19%) Pancreatic islet cell carcinoma: 0/9 (matched control), 0/79 (pooled control), 1/49 (2%), 3/46 (7%) *Females* Adrenal cortical adenoma: 1/10 (10%, matched control), 4/78 (5%, pooled control), 4/47 (9%), 11/42 (26%) Adrenal cortical adenoma or carcinoma (combined): 1/10 (10%, matched control), 4/78 (5%, pooled control), 6/47 (13%), 13/42 (31%) Mammary gland fibroadenoma: 2/10 (20%, matched control), 9/85 (11%, pooled control), 16/50 (32%), 8/50 (16%)	$P = 0.001$ (trend, vs pooled) $P = 0.002$ (highest dose vs pooled) $P < 0.001$ (trend, vs pooled) $P = 0.048$ (trend, vs matched) $P = 0.035$ (lowest dose vs pooled) $P < 0.001$ (highest dose vs pooled) $P = 0.037$ (trend, vs pooled) $P = 0.046$ (highest dose vs pooled) $P = 0.024$ (trend, vs pooled) $P = 0.048$ (highest dose vs pooled) $P = 0.037$ (trend, vs matched) $P = 0.001$ (trend, vs pooled) $P = 0.001$ (highest dose vs pooled) $P = 0.028$ (trend, vs matched) $P < 0.001$ (trend, vs pooled) $P < 0.001$ (highest dose vs pooled) $P = 0.002$ (lowest dose vs pooled) Cochran-Armitage trend test and Fisher exact test (for pairwise comparison)	Study limited by adaptation of dose levels to observed toxicity during study, and the use of a small number of matched controls Pooled controls: matched controls from study on parathion were combined with matched controls from long-term studies on azinphosmethyl, captan, chloramben, chlordane, dimethoate, heptachlor, malathion, and pichloram

Table 3.2 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence (%) of tumours	Significance	Comments
Sprague-Dawley (M, F) ≤ 120 wk EPA (1984)	Diets containing parathion (purity, 95.11%) at 0 (control), 0.5, 5.0, or 50 ppm for up to 120 wk 60 M and 60 F weanling rats/group (age at start, NR)	*Males* Thyroid follicular cell adenoma[a]: 1/59 (2%), 1/58 (2%), 2/58 (3%), 5/58 (9%) [4/58, 6.9%]	[NS] (see comments)	A histopathological re-evaluation of thyroid and parathyroid glands performed 2 years after the original report noted only four follicular cell adenomas at the highest dose (EPA, 1986a) as opposed to five identified in the first histopathological evaluation (EPA, 1984). In addition, no increase in the incidence of thyroid gland hyperplasia, and no carcinomas were reported
Wistar (M, F) 26 mo EPA (1989a, b)	Parathion (purity, 96.7%) in the feed at concentrations of 0 (control), 2, 8, and 32 ppm to give doses of 0, 0.1, 0.42, and 1.75 mg/kg bw (M) and 0, 0.14, 0.53 and 2.47 mg/kg bw (F) for 26 mo 50 M and 50 F rats (age, 5–6 wk)/group	*Males* Pancreas:[b] Exocrine adenoma: 0/50*, 0/50, 1/49 (2%), 3/50 (6%) Exocrine carcinoma: 0/50, 0/50, 0/49, 1/50 (2%) Exocrine adenoma or carcinoma (combined): 0/50**, 0/50, 1/49 (2%), 4/50 (8%) Islet cell adenoma: 0/50***, 0/50, 1/49 (2%), 3/50 (6%) *Females* No increase in tumour incidence	*P = 0.002 (trend, Cochran Armitage) **P = 0.0022 (trend, Peto test) ***P = 0.007 (trend, Cochran Armitage)	

Table 3.2 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence (%) of tumours	Significance	Comments
Sprague-Dawley (F) ≤ 28 mo Cabello et al. (2001)	Subcutaneous injection of parathion at a dose of 0 (saline control), or 250 µg/100 g bw, injected twice per day for 5 days, and then observed for 28 mo 70 (age, 39 days)/group	Mammary gland adenocarcinoma: 0/70, 10/70 (14%)	[$P < 0.002$, Fisher exact test]	Body weight and survival, NR Rats developing mammary tumours were killed 1 mo after first mammary tumour detected by palpation Tumour latency, 490–619 days The examination of lungs, heart, intestinal tract, ovaries, and uterus did not show any tumour s [the authors did not report how these tissues were examined]

[a] Historical controls: 3.9% (range, 0–8.0%)

[b] Historical controls in male Wistar rats: pancreatic islet cell tumours, 0–6%; exocrine adenomas, 0–6%

bw, body weight; F, female; M, male; mo, month; NR, not reported; NS, not significant; TWA, time-weighted average; wk, week

any tumours. [The Working Group noted the small number of rats tested, the limited number of organs examined by histopathology, and the limited reporting of the study.]

Barnes & Denz (1951) described a study in which three groups of 36 male and 36 female albino rats [strain not reported] (age, 6 weeks) were given diets containing parathion (purity, 76.8%) at a concentration of 10, 20, or 50 ppm for 6 days per week for up to 12 months. Two additional groups of 36 male and 36 female rats were given parathion at 75 or 100 ppm for 27 and 19 days, respectively; these animals were observed for up to 12 months. A control group of 30 males and 30 females was observed for 12 months. The survival rates were 98%, 97%, 97%, and 61% in the groups at 0, 10, 20, and 50 ppm, respectively. Mortality rates during the dosing period were 82% in the group at 75 ppm and 90% in the group at 100 ppm. Histopathological examination was performed on all rats at 75 or 100 ppm, and on 20% of rats in the groups at 0, 10, 20, or 50 ppm, and that were still alive after 12 months. With the exception of a spindle cell sarcoma of the mediastinum in one rat at 20 ppm, no tumours were observed. [The Working Group noted the high mortality in the two groups at the higher doses, the short duration of the exposure and observation periods, the small number of rats undergoing histopathological examination, and the limited reporting of the study.]

In a study by the United States National Toxicology Program, groups of 50 male and 50 female Osborne-Mendel rats (age, 5 weeks), were fed diets containing parathion (purity, 99.5%; impurities unspecified) (NTP, 1979). Male rats initially received parathion at 40 ppm (lower dose) or 80 ppm (higher dose) for 13 weeks, then doses were lowered to 30 ppm (lower dose) and 60 ppm (higher dose) for 67 weeks, resulting in time-weighted average doses of 32 ppm (lower dose) and 63 ppm (higher dose). Female rats initially received parathion at 20 ppm (lower dose) or 40 ppm (higher dose) for 13 weeks, then doses were increased to 30 ppm (lower dose) and 60 ppm (higher dose) for 21 weeks (to be consistent with the doses for male rats); but then lowered to 20 ppm (low dose) and 40 ppm (high dose) for 46 weeks (due to generalized tremors among females at the higher dose after 33 weeks), resulting in time-weighted average doses of 23 ppm (lower dose) and 45 ppm (higher dose). All rats were subsequently observed for 32–33 weeks. A matched control group of 10 males and 10 females was observed for 112 weeks, while a pooled group of 90 males and 90 females served as controls for the statistical analysis. Matched controls from the study on parathion were combined with matched controls from long-term studies performed at the same laboratory on azinphosmethyl, captan, chloramben, chlordane, dimethoate, heptachlor, malathion, and picloram. At the end of the study, survival in the groups at the higher dose was 72% in males and 68% in females, while survival in the groups at the lower dose was 62% in males and 72% in females. In the matched control group, a survival rate of 70% was recorded for males and females. Full histopathology was performed.

In males, the incidence of adrenal cortical adenoma or carcinoma (combined) was 3/80 (4%) in pooled controls, 0/9 in matched controls, 7/49 (14%) in the group at the lower dose (two rats developed carcinoma), and 11/46 (24%) in the group at the higher dose (two rats developed carcinoma) (Cochran-Armitage test for positive trend: $P < 0.001$ using pooled controls, $P = 0.048$ using matched controls; Fisher exact test: high-dose group versus pooled controls, $P < 0.001$, and low-dose group versus pooled controls, $P = 0.035$). The incidence of adrenal cortical adenoma was 2/80 (3%) in pooled controls, 0/9 in matched controls, 5/49 (10%) in the group at the lower dose and 9/46 (20%) in the group at the higher dose (Cochran-Armitage test for positive trend: $P = 0.001$ using pooled controls; Fisher exact test: higher-dose versus pooled controls, $P = 0.002$).

In females, the incidence of adrenal cortical adenoma or carcinoma (combined) was 4/78 (5%) in pooled controls, 1/10 (10%) in matched controls, 6/47 (13%) in the group at the lower dose (two rats developed carcinoma), and 13/42 (31%) in the group at the higher dose (two rats developed carcinoma) (Cochran-Armitage test for positive trend: $P < 0.001$ using pooled controls, $P = 0.028$ using matched controls; Fisher exact test: high-dose group versus pooled controls, $P < 0.001$).

In males, the incidence of islet cell carcinoma of the pancreas was 0/79 in pooled controls, 0/9 in matched controls, 1/49 (2%) in the group at the lower dose, and 3/46 (7%) in the group at the higher dose (Cochran-Armitage test for positive trend: 0.024 using pooled controls; Fisher exact test: high-dose group versus pooled controls, $P = 0.048$). Follicular cell adenoma of the thyroid gland was also observed, with incidences of 5/76 (7%) in pooled controls, 3/10 (30%) in matched controls, 2/46 (4%) in the group at the lower dose, and 8/43 (19%) in the group at the higher dose (Cochran-Armitage test for positive trend: $P = 0.037$ using pooled controls; Fisher exact test: higher-dose group versus pooled controls, $P = 0.046$). In females, there was a significant increase ($P = 0.002$) in the incidence of fibroadenoma of the mammary gland in the group at the lower dose (16/50; 32%) compared with pooled controls (9/85; 11%) (NTP, 1979). [The Working Group noted the adaptation of dose levels because of observed toxicity, and the use of small numbers of matched controls.]

A report by the EPA (1984) provided information on a study in which diets containing parathion (purity, 95.11%) were given to groups of 60 male and 60 female weanling Sprague-Dawley rats [age at start, not reported] at a concentration of 0 (control), 0.5, 5, or 50 ppm for up to 120 weeks. Mortality in all groups was similar by the end of the study. Body-weight gain was decreased in males and females in the group at the highest dose. Follicular cell adenoma of the thyroid gland was observed at a [non-significantly] higher incidence in the groups of treated males compared with controls: 1/59 (2%, control), 1/58 (2%), 2/58 (3%), 5/58 (9%) [4/58; 6.9%]. The EPA (1986a) indicated that the historical incidence for this tumour in male Sprague-Dawley rats at this laboratory ranged from 0% to 8.0% (mean, 3.9%). No other increase in tumour incidence was reported. Two years after the original report, a re-evaluation of the histopathology of the thyroid and parathyroid glands was performed and published (EPA, 1986a). The re-evaluation was considered necessary owing to the lack of increase in the incidence of hyperplasia of the thyroid gland reported in the group at the highest dose. [Such an increase may precede the appearance of neoplastic changes.] A re-evaluation of the histology slides by an expert in endocrine pathology reported only four follicular cell adenomas of the thyroid in the group at the highest dose, as opposed to five as identified in the original histological evaluation. No follicular carcinomas of the thyroid were reported.

The EPA (1989a, b) also provided information on a study in which groups of 50 male and 50 female Wistar rats (age, 5–6 weeks) were given diets containing parathion (purity, 96.7%) at a concentration of 0 (control), 2, 8, or 32 ppm for 26 months. There was a treatment-related increase in mortality in females at the highest dose, while mortality in all other groups was similar at termination of the study. A decrease in body-weight gain was observed in males and females at the highest dose. There was a significant positive trend in the incidence of tumours of the pancreas in male rats; the incidences of exocrine adenoma were: 0/50, 0/50, 1/49 (2%), 3/50 (6%) ($P = 0.002$, Cochran Armitage test); the incidences of exocrine adenoma or carcinoma (combined) were: 0/50, 0/50, 1/49 (2%), 4/50 (8%) ($P = 0.0022$, Peto test); and the incidences of islet cell adenoma were: 0/50, 0/50, 1/49 (2%), 3/50 (6%) ($P = 0.007$, Cochran Armitage test). No other increases in tumour incidence were reported.

An additional study in rats treated by gavage was found to be inadequate for the evaluation of parathion by the Working Group because a mixture of 15 pesticides (including only 0.70% parathion) was studied (Pasquini et al., 1994).

3.2.2 Subcutaneous administration

Cabello et al. (2001) carried out an experiment on 140 virgin female Sprague-Dawley rats (age, 39 days); 70 rats were treated subcutaneously with saline, while an additional 70 rats were treated with parathion (250 µg/100 g bw) twice per day for 5 days, and observed for 28 months. Changes in body weight and survival were not reported. Rats with tumours of the mammary gland were killed at 1 month after detection of the tumour by palpation. Tumours were examined by light microscopy. At termination of the experiment, rats in the control group did not develop any type of tumour, while 10 out of 70 (14%) rats treated with parathion developed adenocarcinoma of the mammary gland [$P = 0.002$]. Tumour latency was 490–619 days.

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

Extensive literature was available on the toxicokinetics of parathion in humans and experimental animals.

4.1.1 Absorption

(a) Humans

The evidence for absorption and internal exposure to organophosphate pesticides, such as parathion, has been documented in a large number of biomonitoring studies in humans (e.g. Arcury et al., 2007). For example, *para*-nitrophenol, a metabolic by-product of parathion, was detectable in the urine of children aged ≤ 6 years in a central Washington State agricultural community (Fenske et al., 2002).

Acute poisoning episodes in humans also confirm that parathion can be absorbed from the gastrointestinal tract (Hoffmann & Papendorf, 2006).

Specific data on rates of oral absorption or fractional uptake in humans were not available but on the basis of depressed blood cholinesterase activities and the detection of urine metabolites of parathion in intoxicated patients, absorption of parathion does occur via the gastrointestinal tract (Areekul et al., 1981; Olsson et al., 2003). [The Working Group noted that, because of its lipophilicity, parathion is expected to be absorbed via passive diffusion.] On the basis of biomonitoring studies of parathion in humans, dermal and oral exposures during occupational practices and diet are important routes of exposure, whereas inhalation appears to be less important (Alavanja et al., 2013).

Several studies were identified that examined dermal penetration of parathion in a variety of different model systems. Parathion was not efficiently absorbed into the body after dermal contact under controlled experimental settings (Qiao et al., 1994; Wester et al., 2000; van der Merwe & Riviere, 2005). Only a small fraction of the dermally applied parathion dose to human skin was absorbed and bioavailable. The rate-limiting step during percutaneous absorption appeared to be the partitioning of parathion into the stratum corneum (Qiao et al., 1994).

Dermal uptake can be affected by parathion formulation, ambient temperature, relative humidity, and airflow across the exposed skin (Durham et al., 1972). The extent of absorption of parathion after dermal exposure, assessed by measurements of parathion on pads worn by workers on clothing near bare skin, was significantly influenced by the ambient temperature. The excretion of *para*-nitrophenol (parathion metabolite) in urine increased as a function of

the ambient temperature, indicating enhanced dermal absorption of parathion.

In controlled experiments to separately assess respiratory and dermal absorption among orchard workers engaged in applying parathion using power airblast spray equipment, and wearing either protective clothing or a respirator during exposure, dermal absorption proved to be much greater (0.497–0.666 mg of the absorbed dose) than respiratory absorption (0.006–0.088 mg of the absorbed dose), based on excretion of the parathion metabolite *para*-nitrophenol (Durham et al., 1972).

Clinical reports of severe intoxication with parathion indicated that there were large differences in plasma levels of parathion and paraoxon between the patients, suggesting inter-individual differences in absorption, metabolism, or excretion (Eyer et al., 2003). The estimated amount of parathion that was absorbed varied widely (range, 0.12–4.4 g).

(b) Experimental systems

There was rapid absorption of parathion in male Wistar rats given parathion orally (at one third of the median lethal dose, LD_{50}), as shown by detection of parathion in the blood within minutes after administration (Garcia-Repetto et al., 1995).

The peak serum concentrations in six mongrel dogs treated orally with parathion at a dose of 10 mg/kg bw varied from 0.02 to 0.41 µg/mL, while time to peak concentration ranged from 30 minutes to 5 hours, indicating substantial inter-individual variability in oral absorption (Braeckman et al., 1983).

A toxicokinetic study of parathion in rabbits given a single oral exposure of parathion (3 mg/kg bw) showed that the first-order rate constant of oral parathion absorption was 33 h^{-1} (Peña-Egido et al., 1988a), which indicates that absorption from the gastrointestinal compartment is rapid and that parathion in this compartment has a half-life of 1.3 minutes. In rabbits, the rates of dermal absorption per unit area were estimated to be 0.059 µg/minute per cm^2 of skin for parathion and 0.32 µg/minute per cm^2 for paraoxon; these are much slower than rates of uptake after oral absorption (Nabb et al., 1966).

In pigs, the rate of dermal absorption was significantly influenced by the vehicle used. Absorption of parathion ranged from 15% to 30% of the applied dose when administered in dimethylsulfoxide or octanol, while only 4–5% of the applied dose was absorbed when administered in macrogol. The type of surfactant in the formulation under consideration also significantly influences rates of dermal absorption (Gyrd-Hansen et al., 1993).

The extent of absorption after dermal application of parathion using a porcine skin in-vitro model was 1–3% of the applied dermal dose (van der Merwe & Riviere, 2005).

4.1.2 Distribution

(a) Humans

No data on tissue distribution beyond blood concentrations of parathion in humans were available to the Working Group. After intoxication with parathion, measurement of plasma concentrations of parathion indicated that the volume of distribution at steady-state (V_{dss}) for parathion was around 20 L/kg, suggesting a wide distribution (Eyer et al., 2003). Several studies have suggested that 94–99% of parathion is protein-bound at equilibrium, mostly to serum albumin (Braeckman et al., 1983; Nielsen et al., 1991; Foxenberg et al., 2011). In-vitro equilibrium dialysis experiments indicated that once equilibrium had been reached (in about 60 minutes), affinity for human serum albumin was greater for parathion (~94% bound) than for paraoxon (~60% bound) (Foxenberg et al., 2011).

(b) Experimental systems

After absorption, parathion is uniformly distributed systemically in rodents, with no evidence of long-term accumulation in any particular tissue, including fat (Hazleton & Holland, 1950). After absorption in rats injected subcutaneously with [^{32}P]-labelled parathion, radioactive material is readily taken up by the liver, kidney, and fat (Fredriksson & Bigelow, 1961), and metabolized. Available in-vivo data in rats show that parathion has an affinity for adipose tissue and the liver (Poore & Neal, 1972; Garcia-Repetto et al., 1995), which is supported by studies in rat and mouse tissues in vitro (Sultatos et al., 1990; Jepson et al., 1994). In male Sprague-Dawley rats given a single oral dose of [^{35}S]-labelled parathion (29 mg/kg bw), the tissue levels of radiolabel 35 minutes after dosing followed the rank order: liver > intestine > kidney > muscle > lung (Poore & Neal, 1972). [The Working Group noted that adipose tissue was not examined in this particular study.]

In rats, the time-course for parathion in blood after administration of an intravenous dose of parathion showed a rapid distribution phase, followed by a slower elimination phase (Eigenberg et al., 1983). The time-course of parathion levels in liver and brain followed the same kinetic profile as in blood. Rapid metabolism of parathion in liver was evident. The elimination half-life of parathion in the blood was 3.4 hours after an intravenous dose (3 mg/kg bw) in rats. Three to four times higher levels of paraoxon were found in weanling rat brain than in adult rat brain after intravenous administration of parathion to immature (age, 23 days) and adult (age, 60–75 days) rats (Gagné & Brodeur, 1972).

4.1.3 Metabolism

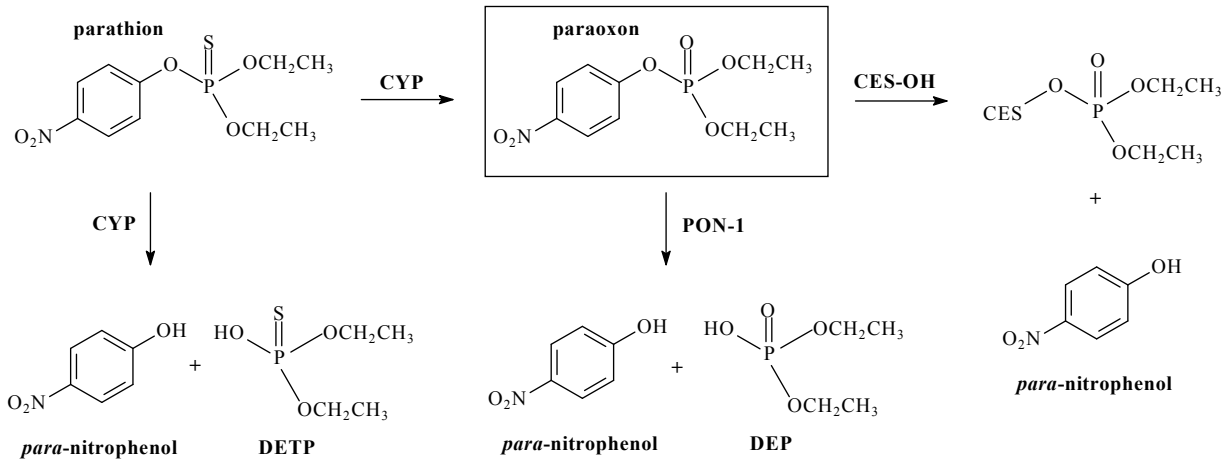
(a) Overview of the metabolism of parathion

Cytochrome P450s (CYPs) are important enzymes for the bioactivation and detoxification of parathion, as are paraoxonase-1 and carboxylesterase for the detoxification of the active paraoxon metabolite (see the pathways of metabolism of parathion outlined in Fig. 4.1). The bioactivation and detoxification pathways controlled by CYPs share a common phosphooxythiran intermediate (see Fig. 4.2; Neal & Halpert, 1982). In general, a complex picture emerges regarding the metabolism of organophosphorothioates. Multiple CYP isoforms are involved in their oxidation. Human CYP3A4/5, CYP2C8, and CYP1A2 have been identified as being involved in the metabolism of parathion (Mutch & Williams, 2006). During oxidative metabolism of parathion by CYP, the release of the sulfur atom from parathion leads to covalent modification of cysteine residues and a resulting loss of the haem moiety, thereby inactivating the CYP (Halpert et al., 1980).

Carboxylesterases (which are abundant esterases and members of the serine hydrolase superfamily) and paraoxonase-1 are found in the liver and plasma, and are important enzymes involved in paraoxon detoxification in several species, including humans (Ross et al., 2012; Costa et al., 2013), mice and rats (Crow et al., 2007), and rainbow trout (Abbas & Hayton, 1997). It is notable that humans express abundant amounts of carboxylesterase in the liver, but do not express carboxylesterase in the plasma as do rodents (Li et al., 2005). Paraoxonase-1 can catalytically hydrolyse the oxon (Costa et al., 2013), while carboxylesterases are 1:1 stoichiometric scavengers of oxons, which do not catalytically hydrolyse the substrate (Crow et al., 2012).

The oxon metabolite can also escape the scavenging function of carboxylesterase and instead covalently modify (and inhibit) various serine hydrolase enzymes, including the B-esterase

Fig. 4.1 Biotransformation of parathion



Cytochrome P450 (CYP)-catalysed reactions produce the desulfuration metabolite (oxon) or aryl alcohol and dialkylthiophosphate products. Paraoxonase-1 (PON-1) and carboxylesterase (CES) contribute to parathion detoxification reactions. The bioactive paraoxon metabolite is indicated by the box. 4-Nitrophenol is the dearylation product and the major metabolite of parathion. CES-OH, indicates carboxylesterase with –OH being the functionality of the active-site serine residue that is covalently modified by oxon metabolite.
DEP, diethyl phosphate; DETP, diethylthiophosphate
Compiled by the Working Group using information from Eaton (2000) and Poet et al. (2004)

targets butyrylcholinesterase, acetylcholinesterase, and carboxylesterase (Casida & Quistad, 2004; see Fig. 4.3). In general, analytical measurement of oxons in blood is difficult due to the low levels and relative instability of the metabolite formed (Timchalk et al., 2007). The most important target with respect to the insecticidal action of the oxon is acetylcholinesterase, the esterase responsible for terminating the signalling action of the neurotransmitter acetylcholine in the central and peripheral nervous systems.

(b) Humans

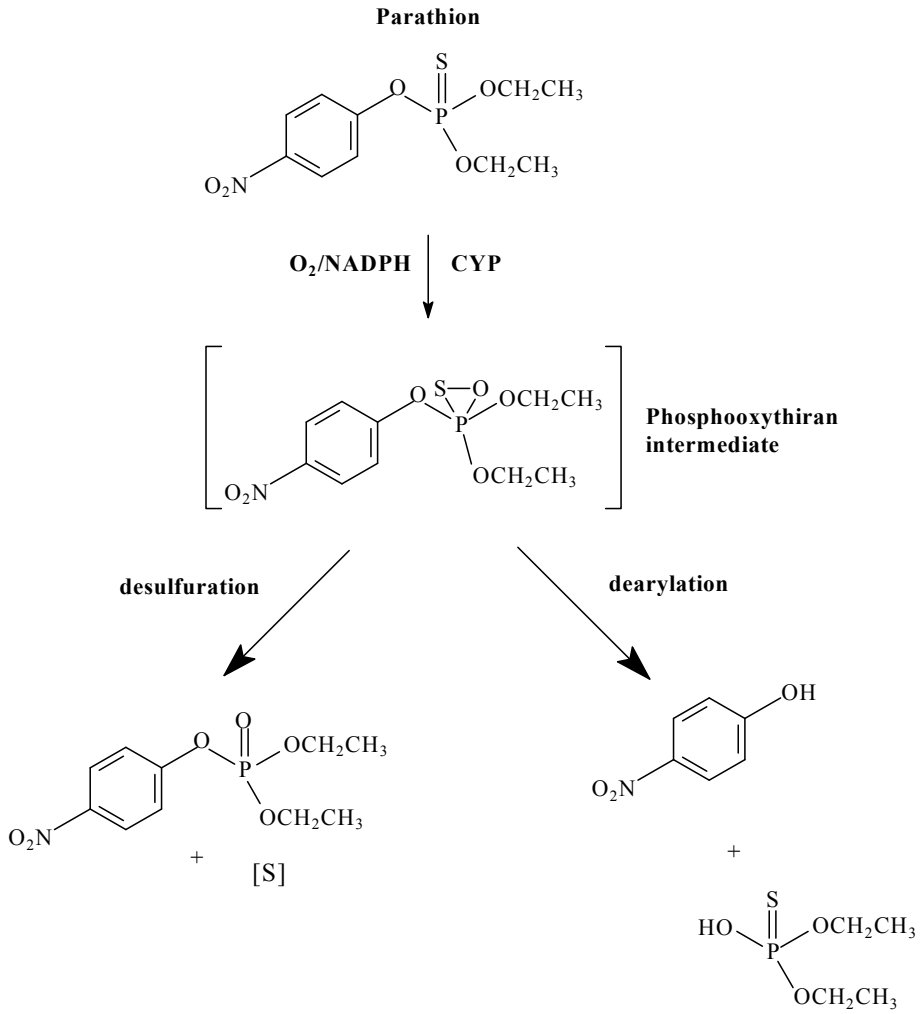
The metabolism of parathion in humans follows the pathways outlined in Fig. 4.1. Rates of parathion oxidation varied about 10-fold in human liver microsomes from 23 individuals (1.72–18.33 nmol total metabolites/mg protein per minute) (Butler & Murray, 1997). CYP3A4 was implicated as a major CYP isoform responsible for the oxidation of parathion. Desulfuration of parathion can result in substantial inhibition of CYP due to transfer of the phosphorothioate thionosulfur atom to the CYP apoprotein, resulting in amino acid modification and enzyme inactivation (Butler & Murray, 1997).

(c) Experimental systems

Metabolism by cytochrome P450s in liver is an important pathway of parathion detoxification in rodents. In-vivo inhibition of CYP3A in rat liver by neostigmine or physostigmine significantly increased the area under the curve (AUC) for parathion in blood, while substantially reducing its clearance (Hurh et al., 2000a, b). Braeckman et al. (1983) estimated an 82–97% hepatic extraction ratio in anaesthetized dogs given an intravenous dose of parathion in the foreleg vein, which emphasizes the efficient metabolism of parathion by the liver.

Compared with adult male rats, adult female rats exhibited a reduced capacity to metabolize parathion through the bioactivation and dearylation pathways (Gagné & Brodeur, 1972). In the same study, weanling rats were less capable of detoxifying parathion and paraoxon than were adults.

Fig. 4.2 Common CYP-derived phosphooxythiran intermediate of parathion



Phosphooxythiran can decompose to paraoxon and a sulfur atom [S] (desulfuration pathway) or to *para*-nitrophenol and diethylthiophosphate (dearylation pathway)
CYP, cytochrome P450
Compiled by the Working Group using information from Neal & Halpert (1982)

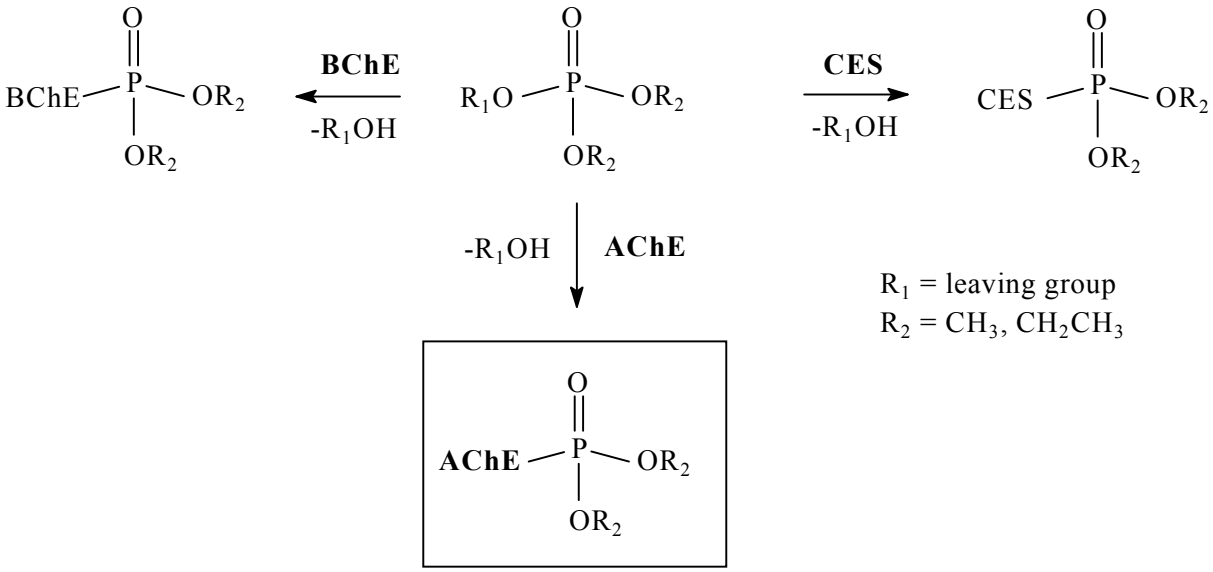
Extrahepatic metabolism of parathion has been demonstrated in two studies. Isolated perfused lungs from guinea-pigs and rabbits were shown to efficiently extract parathion and paraoxon from the perfusate solution, enabling biotransformation of the compounds in the lung tissue (Lessire et al., 1996). There was also evidence for first-pass metabolism of parathion by isolated porcine skin after topical application (Chang et al., 1994). Conversion to paraoxon and *para*-nitrophenol was noted.

4.1.4 Excretion

(a) Humans

The polar metabolites of parathion are excreted primarily via the kidney into the urine. For example, *para*-nitrophenol, DEP, and DETP are found in human urine after exposure to parathion, and have been used for biomonitoring purposes (Arterberry et al., 1961; Wolfe et al., 1970; Morgan et al., 1977). *Para*-Nitrophenol is excreted as glucuronide or sulfate conjugates in

Fig. 4.3 Reactions of a generic oxon metabolite with esterases



Reaction product with the canonical toxicological target of organophosphate responsible for neurotoxicity is shown in box; AChE, acetylcholinesterase; BChE, butyrylcholinesterase; CES, carboxylesterase
Adapted with permission from Casida & Quistad (2004); copyright (2004) American Chemical Society

the urine (Elliott et al., 1960). Larger amounts of parathion metabolites (DEP and DETP) were detectable in the urine of children of farmworkers in North Carolina when compared with reference data for the USA (Arcury et al., 2006). Metabolic degradates of parathion have also been detected in amniotic fluid (Bradman et al., 2003).

(b) Experimental systems

DETP, DEP, and *para*-nitrophenol were detected in the urine of male Sprague-Dawley rats given parathion by oral gavage (0.032 or 0.32 mg/rat per day) once per day for 3 days (Bradway et al., 1977). The dialkyl(thio)phosphate degradates of parathion, DEP and DETP, can also be readily absorbed after oral exposure in rats and are rapidly excreted unchanged in the urine (Timchalk et al., 2007). When DEP or DETP were administered orally by gavage to male Sprague-Dawley rats, peak plasma concentrations were reached 1–3 hours after administration. By 72 hours after dosing, essentially all DEP was recovered in the urine, suggesting minimal metabolism, while 50% of the administered dose of DETP was recovered in the urine (Timchalk et al., 2007).

The urinary excretion kinetics of the metabolite *para*-nitrophenol were studied in rabbits given parathion as an oral dose of 3 mg/kg bw (Peña-Egido et al., 1988b). Elimination of *para*-nitrophenol began rapidly and, of the total amount excreted during the study period, 46% was excreted in the first 3 hours; 85% was excreted 6 hours after administration of parathion. After topical application of [^{14}C]-labelled parathion (200 µg) to weanling Yorkshire sows, > 80% of the absorbed radiolabel was eliminated in the urine (Carver & Riviere, 1989). In another study in pigs, intravenous administration of [^{14}C]-labelled parathion at 0.5 mg/kg bw resulted in urinary excretion of 18%, 48%, and 82% of the administered dose within 3 hours in newborn, 1-week-old, and 8-week-old piglets, respectively, suggesting age-dependent excretion of parathion (Nielsen et al., 1991). The main metabolite

detected was *para*-nitrophenyl-glucuronide, which comprised 85% of the [^{14}C]-labelled material in the urine.

4.2 Mechanisms of carcinogenesis

This section summarizes evidence for the key characteristics of carcinogens (IARC, 2014) for which there were adequate data for evaluation, concerning whether parathion is genotoxic; modulates receptor-mediated effects; induces oxidative stress; induces chronic inflammation; and alters cell proliferation, death or nutrient supply.

4.2.1 Genotoxicity and related effects

Parathion has been studied in several assays for genotoxicity in different test systems. Table 4.1, Table 4.2, Table 4.3, Table 4.4 and Table 4.5 summarize the studies carried out in exposed humans, in human cells in vitro, in non-human mammals in vivo and in vitro, and in non-mammalian systems in vitro, respectively.

(a) Humans

See Table 4.1 and Table 4.2

In 25 male vegetable-garden workers exposed occupationally to seven pesticides, including parathion, the frequency of chromosomal aberration and sister-chromatid exchange was increased in peripheral lymphocytes when compared with controls (Rupa et al., 1988).

In human liver HepG2 cell cultures, parathion induced DNA damage as measured by the comet assay (Edwards et al., 2013). Parathion caused sister-chromatid exchange in the lymphoid cell line LAZ-007, with or without metabolic activation (Sobti et al., 1982), but not in cultured human lymphocytes with or without metabolic activation (Kevekordes et al., 1996). Parathion did not cause unscheduled DNA synthesis in human fetal lung fibroblasts, WI-38 (Waters et al., 1980).

Paraoxon, a metabolite of parathion, induced DNA strand breaks in lymphocytes from adult peripheral blood and from newborn umbilical cord blood, with a dose–response relationship; induction was greater in newborns than in adults. Paraoxon also increased the frequency of micronucleus formation in human lymphocytes from adults and newborns (Islas-González et al., 2005; Rojas-García et al. 2009).

(b) Experimental systems

See Table 4.3, Table 4.4, Table 4.5

Parathion did not cause dominant lethal mutation in mice after oral administration (Waters et al., 1980). Parathion also failed to induce micronucleus formation in mouse bone marrow after a single oral (Kevekordes et al., 1996) or intraperitoneal (EPA, 1988) dose; however, micronucleus formation was induced by repeated intraperitoneal doses (Ni et al., 1993).

Parathion induced micronucleus formation in Chinese hamster lung cells (Ni et al., 1993). Parathion also induced sister-chromatid exchange in Chinese hamster ovary cells; the metabolite paraoxon also induced sister-chromatid exchange, with a stronger effect (Nishio & Uyeki, 1981). Parathion did not cause sister-chromatid exchange in rat primary hepatocytes, nor did it show a clear mutagenic effect in the *Hprt* test in Chinese hamster ovary cells (EPA, 1988).

Parathion did not cause mutations in *Drosophila melanogaster* (Waters et al., 1980).

Parathion did not induce mutations in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 (Bartsch et al., 1980; EPA, 1988). Paraoxon, a metabolite of parathion, did not induce mutation in *Salmonella typhimurium* YG1024 with metabolic activation (Wagner et al., 1997), but caused forward mutation in *Schizosaccharomyces pombe* (ade6) without metabolic activation (Gilot-Delhalle et al., 1983).

Table 4.1 Genetic and related effects of parathion in exposed humans

End-point	Test	Tissue	Cell type (if specified)	Description of exposed and controls	Response[a], significance	Comments	Reference
Chromosomal damage	Chromosomal aberrations	Blood	Lymphocytes	25 male workers in vegetable gardens, smokers and alcohol consumers, exposed to 7 pesticides, including parathion 30 controls, healthy males from the same age group and socioeconomic class (control I, 20 non-smokers and non-consumers of alcohol; control II, 10 smokers and alcohol consumers)	(+), $P < 0.05$	Exposure to several pesticides; P value for exposed workers, irrespective of the duration of exposure, compared with control group I or II	Rupa et al. (1988)
Chromosomal damage	Sister-chromatid exchanges	Blood	Lymphocytes	25 male workers in vegetable gardens, smokers and alcohol consumers, exposed to 7 pesticides, including parathion 30 controls, healthy males from the same age group and socioeconomic class (control I, 20 non-smokers and non-consumers of alcohol; control II, 10 smokers and alcohol consumers)	(+), $P < 0.05$	Exposure to several pesticides; P value for exposed workers, irrespective of the duration of exposure, compared with control group I or II	Rupa et al. (1988)

[a] +, positive

Table 4.2 Genetic and related effects of parathion and paraoxon in human cells in vitro

Tissue, cell line	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Parathion							
Liver, HepG2	DNA damage	DNA strand break Comet assay	+	NT	12 mM [5242 µg/mL]		Edwards et al. (2013)
Fetal lung fibroblasts (WI-38)	DNA damage	Unscheduled DNA synthesis	–	–	NR		Waters et al. (1980)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	–	–	100 µM [29 µg/mL]		Kevekordes et al. (1996)
Lymphoid cell line (LAZ-007)	Chromosomal damage	Sister-chromatid exchange	+	+	0.2 µg/mL without, and 20 µg/mL with metabolic activation	Only one concentration tested [20 µg/mL] with metabolic activation	Sobti et al. (1982)
Paraoxon							
Lymphocytes (adult peripheral blood or newborn umbilical cord blood)	DNA damage	DNA strand breaks, comet assay	+	NT	0.075 µg/mL	No statistical calculations	Islas-González et al. (2005)
Lymphocytes (blood)	Chromosomal damage	Micronucleus formation	+	NT	1 µM [0.29 µg/mL]	Positive dose–response relationship (1–25 µM)	Rojas-García et al. (2009)
Lymphocytes (adult peripheral blood or newborn umbilical cord blood)	Chromosomal damage	Micronucleus formation	+	NT	0.2 µg/mL		Islas-González et al. (2005)

[a] +, positive; –, negative

HepG2, human hepatocellular carcinoma cell line; HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested; NR, not reported

Table 4.3 Genetic and related effects of parathion in non-human mammalian experimental systems in vivo

Species	End-point	Test	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse	Mutation	Dominant lethal test	Ovary/uterus after mating	(–)	10 mg/kg	NA	Only one dose tested; no detailed data available (abstract only)	Degraeve et al. (1979)
Mouse	Mutation	Dominant lethal test	Ovary/uterus after mating	–	250 mg/kg diet	Three doses tested: 62.5, 125, 250 mg/kg diet, p.o. ×1	The index of dead implants per total implants was evaluated after mating	Waters et al. (1980)
Mouse	Chromosomal damage	Micronucleus formation	Bone marrow	–	2.2 mg/kg bw (male), 1.5 mg/kg bw (female)	p.o. ×1	Only one dose tested per sex: highest tolerated dose	Kevekordes et al. (1996)
Mouse	Chromosomal damage	Micronucleus formation	Bone marrow	+	0.1, 0.2, 0.4, 0.8 × LD_{50}	i.p. 1×/day, ×4	LD_{50} not given; LED not specified	Ni et al. (1993)
Mouse	Chromosomal damage	Micronucleus formation	Bone marrow	–	26 mg/kg bw	i.p. ×1		EPA (1988)

[a] +, positive; –, negative; (–), negative, no detailed data available

HID, highest ineffective dose; i.p., intraperitoneal; LD_{50}, median lethal dose; LED, lowest effective dose, NA, not available; NT, not tested; p.o., oral

Table 4.4 Genetic and related effects of parathion and paraoxon in non-human mammalian cells in vitro

Species	Tissue, cell line	End-point	Test	Results[a]		Concentration (LEC/HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Parathion								
Hamster	Chinese hamster ovary cells	Mutation	*Hprt*	+/–	+/–	0.03 µL/mL	No effect at a higher dose (0.3 µL/mL); equivocal results	EPA (1988)
Hamster	Chinese hamster ovary cells	Chromosomal damage	Sister-chromatid exchange	+	NT	0.3 mM [87.5 µg/mL]		Nishio & Uyeki (1981)
Rat	Primary hepatocytes	DNA damage	Unscheduled DNA synthesis	–	NT	0.003 µL/mL		EPA (1988)
Hamster	Chinese hamster lung	Chromosomal damage	Micronucleus formation	+	NT	NR	Only one dose tested: highest dose that induced 50% of cell death [50% toxicity], NR	Ni et al. (1993)
Paraoxon								
Hamster	Chinese hamster ovary cells	Chromosomal damage	Sister-chromatid exchange	+	NT	0.1 mM [27.5 µg/mL]	Produced a higher frequency of exchange than parathion	Nishio & Uyeki (1981)

[a] +, positive; –, negative; +/–, equivocal

HIC, highest ineffective concentration; Hprt, hypoxanthine-guanine phosphoribosyltransferase; LEC, lowest effective concentration; NR, not reported; NT, not tested

Table 4.5 Genetic and related effects of parathion and paraoxon in non-mammalian systems

Phylogenetic class	Test system	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Parathion								
Insect	*Drosophila melanogaster*	Mutation	Sex-linked recessive lethal	–	NA	0.5 ppm [0.5 µg/mL]		Waters et al. (1980)
Prokaryote (bacteria)	*Salmonella typhimurium* TA98, TA100	Mutation	Reverse mutation	–	–	1.35 µmol/plate [372 µg/plate]		Bartsch et al. (1980)
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Mutation	Reverse mutation	–	–	10 000 µg/plate		EPA (1988)
Paraoxon								
Prokaryote (bacteria)	*Salmonella typhimurium* YG1024	Mutation	Reverse mutation	NT	–	1 mM [275 µg/mL]		Wagner et al. (1997)
Lower eukaryote (yeast)	*Schizosaccharomyces pombe* (ade6)	Mutation	forward mutation	+	–	12 mM [3300 µg/mL]		Gilot-Delhalle et al. (1983)

[a] +, positive; –, negative
HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested

4.2.2 Receptor-mediated mechanisms

(a) Neurotoxicity-pathway receptors

Parathion is bioactivated to paraoxon in insects and mammals (Section 4.1.3; Casida & Quistad, 2004). Paraoxon can covalently modify the catalytic serine residue of several B-esterases and inhibit their catalytic activity, including the canonical target acetylcholinesterase, resulting in acute neurotoxicity (see Fig. 4.3). Additional receptor targets of parathion and paraoxon that can affect neurotoxicity include butyrylcholinesterase, neuropathy target esterase, and cannabinoid receptor (Quistad et al., 2002). Some studies reviewed in Sections 4.2.4 and 4.2.5 showed that some mechanistic effects of relevance to the carcinogenicity of parathion are blocked or mitigated by co-administration of the anticholinergic drug atropine, and may be at least in part be related to inhibition of acetylcholinesterase activity.

(b) Sex-hormone pathway disruption

(i) Humans

No data from exposed humans were available to the Working Group.

In an in-vitro human androgen-receptor reporter-gene assay using a transfected African monkey kidney cell line (CV-1), parathion (0.1–10 μM) showed significant inhibitory effects on transcriptional activity induced by 5α-dihydrotestosterone (Xu et al., 2008). The concentration for 50% inhibition (IC_{50}) of 5α-dihydrotestosterone-induced chloramphenicol acetyltransferase activity was 0.20 ± 0.04 μM. Parathion did not exhibit androgenic activity. Similarly, in a human androgen-receptor reporter-gene assay in a Chinese hamster ovary cell line (CHO-K1), parathion was an androgen receptor antagonist, and did not exhibit androgen agonist activity (Kojima et al., 2004, 2010).

Parathion was neither an agonist nor an antagonist for human estrogen receptors α or β in similarly constructed transactivation assays in CHO-K1 cells (Kojima et al., 2010). Parathion tested negative for estrogenicity in an estrogen receptor-positive human breast-cancer cell line (MCF-7 BUS), and did not show estrogenic activity in an estrogen receptor-negative breast-cancer cell line (MDA MB 231) (Oh et al., 2007).

(ii) Experimental systems

In vivo

In CF-1 mice, serum testosterone levels were dramatically reduced 1 and 8 days after an intraperitoneal injection of either commercial-grade (9 mg/kg bw) or pure (300 mg/kg bw) parathion (Contreras et al., 2006). In the group receiving commercial-grade parathion levels were still very low at 40 days after injection. Pathological changes in the testes and teratozoospermia were also observed at days 8 and 40.

In castrated immature male Wistar-Imamichi rats treated with testosterone, daily subcutaneous injections of a metabolite of parathion, 4-nitrophenol (see Section 4.1.1), elevated levels of follicle-stimulating hormone and luteinizing hormone in the Hershberger assay at a dose of 0.1 mg/kg for 5 days; there were no effects with 4-nitrophenol at doses of 0.01 or 1.0 mg/kg (Li et al., 2006). There were no observed effects on levels of follicle-stimulating hormone and luteinizing hormone in ovariectomized immature female injected subcutaneously with 4-nitrophenol at a dose of 1, 10, or 100 mg/kg per day for 7 days. In follow-up studies, levels of luteinizing hormone were significantly lowered, while levels of corticosterone were significantly elevated in male rats injected subcutaneously with 4-nitrophenol for 14 days at daily doses 0.01, 0.1, 1 or 10 mg/kg, and levels of follicle-stimulating hormone were low in all groups except at the lowest dose (Li et al., 2009). Plasma levels of inhibin, an inhibitor of follicle-stimulating hormone, were also increased in all groups except at the lowest dose. Levels of testosterone

were elevated above those of controls in all treatment groups, but the increase was statistically significant only at the highest dose.

Early studies explored the potential impact of parathion on steroid metabolism Thomas & Schein (1974). In adult male mice, neither uptake nor metabolism of [^{3}H]-labelled testosterone was significantly affected by prior treatment with parathion. However, levels of [^{3}H]-labelled testosterone were elevated compared with controls (239 ± 37, 260 ± 38, 471 ± 51, and 421 ± 87 dpm/mg in the control group, and groups receiving parathion at 1.3, 2.6, or 5.3 mg/kg, respectively).

In vitro

Parathion (0.01 to 10 μM) significantly inhibited, in a dose-dependent manner, the binding of dihydrotestosterone to cytosol androgen-binding components from prostate, seminal vesicle, kidney, and liver, but not from the intestine (Schein et al., 1980). Parathion (0.4, 4, or 20 μM) also significantly reduced the formation of [^{3}H]-labelled dihydrotestosterone in mouse but not rat prostate gland in vitro (Thomas & Schein, 1974). However, formation of [^{3}H]androstanediol and [^{3}H]androstenedione was strongly affected by exposure to parathion in the rat under the same in-vitro conditions. Using hepatic microsomes from mice treated with parathion, formation of [^{3}H]androstanediol in vitro was elevated for the group at the highest dose. In a later experiment, the in-vitro metabolism of [1,2-^{3}H]testosterone by anterior prostate gland from mice treated with parathion was not altered by this treatment (Thomas et al., 1977).

Production of testosterone in vitro was not significantly altered in Leydig cells harvested 1, 8 or 40 days from CF-1 mice injected intraperitoneally with a single dose of commercial or pure parathion (Contreras et al., 2006), in contrast to findings in vivo (see above). [The Working Group noted that levels of testosterone after 8 and 40 days for treated animals were markedly lower than for controls, but did not meet the authors' significance cut-off of $P < 0.01$.]

Welch et al. (1967) reported that parathion (10 and 100 μM) inhibited hydroxylation of testosterone in rat microsomes.

In fresh liver microsomes from adult male Swiss Webster mice, incubated with added testosterone-4-[^{3}H], parathion at a concentration of 0.1 mM, but not at 0.01 mM, significantly reduced testosterone metabolism (Stevens, 1973). Parathion did not alter the production of progesterone in primary granulosa cells harvested from pig ovaries and cultured in vitro (Haney et al., 1984).

(c) Other receptors

(i) Humans

No data from exposed humans were available to the Working Group.

Parathion acted as an agonist in a human pregnane X receptor (PXR) reporter-gene assay in a CHO-K1 cell line (Kojima et al., 2010).

(ii) Experimental systems

Growth hormone was significantly elevated in the pituitary of male and female rats that received paraoxon at a dose of 0.124 mg/kg bw by intraperitoneal injection daily for 14 days (Cehovic et al., 1972). The same effect on growth hormone was seen with high near-lethal exposures (600 μg/mg kg, daily intraperitoneal injection) over a 3-day period, and prolactin levels were elevated in females.

A series of experiments in rats studied the effects of parathion on melatonin synthesis. In a study by Attia et al. (1991), morning administration of parathion by oral gavage for 6 days significantly elevated nocturnal levels of melatonin in serum and in the pineal gland; levels of *N*-acetyltransferase, which acetylates serotonin, were also elevated, but not levels of hydroxyindole-*O*-methyltransferase, which converts *N*-acetylserotonin to melatonin. In a subsequent study, the *β*-adrenergic receptor antagonist

propranolol abrogated the effects of parathion on *N*-acetyltransferase and on nocturnal levels of serum melatonin (levels of pineal melatonin were not significantly increased by parathion) (Attia et al., 1995). Parathion also significantly reduced nocturnal levels of serotonin, and this was also reversed by propranolol. Levels of hydroxyindole-*O*-methyltransferase, *S*-hydroxytryptophan, and hydroxyindole acetic acid were unaffected by treatment with parathion or propranolol. Attia (2000) concluded that parathion affects serotonin metabolism either by effects on sympathetic innervation to the pineal gland, or on the β-adrenergic receptors in the pinealocyte membrane.

Parathion was not an agonist for the aryl hydrocarbon receptor (AhR) in mouse hepatoma Hepa1c1c7 cells stably transfected with a reporter plasmid containing copies of a dioxin-responsive element (Takeuchi et al., 2008; Kojima et al., 2010).

Parathion was not an agonist for mouse peroxisome proliferator-activated receptors α or γ (PPAR α or γ) reporter-gene assays in CV-1 monkey kidney cells (Takeuchi et al., 2006; Kojima et al., 2010).

4.2.3 Oxidative stress, inflammation, and immunosuppression

(a) Oxidative stress

(i) Humans

No data from exposed humans were available to the Working Group.

In human salivary-gland cells exposed in vitro, paraoxon at 10 μM (a non-cytotoxic concentration) induced superoxide formation as determined by dihydroethidium fluorescence (Prins et al., 2014). In addition, paraoxon at the same concentration induced DNA fragmentation, and expression of glutathione synthetase (*GSS*), superoxide dismutase 2 (*SOD2*), and glutathione *S*-transferases m2 and t2 (*GSTM2* and *GSTT2*) genes. [The Working Group noted the recognized limitations of using dichlorodihydrofluorescein as a marker of oxidative stress (e.g. Bonini et al., 2006; Kalyanaraman et al., 2012), and that the studies that reported this end-point as the sole evidence for oxidative stress should thus be interpreted with caution.] In human liver-derived HepG2 cells, parathion induced a significant increase in cellular accumulation of malondialdehyde at concentrations equal to or below those that affected the viability of HepG2 cells (Edwards et al., 2013). The results of comet assays were consistent with the findings for malondialdehyde.

(ii) Experimental systems

In female Wistar and Norway rats, intraperitoneal injection of paraoxon (0.3, 0.7, 1, or 1.5 mg/kg) lead to a decrease in glutathione levels and in the activity of catalase and glutathione-*S*-transferase in various tissues (Jafari et al., 2012). An increase in superoxide dismutase activity and malondialdehyde levels was also found. The extent of induction of oxidative stress by paraoxon was in the following order: brain > liver > heart > kidney > spleen.

Two studies examined parathion-associated markers of oxidative stress in the hippocampus area of the brain. In a study of female Wistar rats exposed to parathion by inhalation (dose not stated; exposure consisted of four consecutive cycles of 15 minutes exposure/45 minutes clean air) 5 days per week for 2 months, significant elevation in levels of malondialdehyde in the hippocampus (determined by *N*-methyl-2-phenylindol colorimetric assay) was reported (Canales-Aguirre et al., 2012). In male Wistar rats given a single subcutaneous dose of parathion at 15 mg/kg, induction of pro-inflammatory and lipid peroxidation biomarkers was observed in the hippocampus (López-Granero et al., 2013).

In pheochromocytoma PC12 cells, an increase in levels of thiobarbituric-acid reactive

substances was observed when cells were treated with parathion at 30 μM (Slotkin et al., 2007).

(b) Inflammation and immunomodulation

The ability of paraoxon and other organophosphate pesticides to act on nicotinic and muscarinic receptors is well documented, and has been proposed as a mechanism of toxicity that is independent of the inhibition of acetylcholinesterase activity (Pope, 1999). Cholinergic signalling may play an important role in the immune system (Verbout & Jacoby, 2012). Evidence for acetylcholine synthesis, storage, release and breakdown – all elements indicative of a potential signalling role – have been demonstrated in various immune cells, including lymphocytes (Kawashima & Fujii, 2004). The association between exposure to parathion and immunomodulation (e.g. lung hypersensitivity and asthma) has been examined in studies detailed below, and it has been hypothesized that such effects are attributable to the action of organophosphates (i.e. paraoxon) on non-neuronal signalling events involving cholinergic systems in cells of the immune system, and the inhibition of acetylcholinesterase activity (Banks & Lein, 2012).

(i) Humans

No data were available to the Working Group.

(ii) Experimental systems

In vivo

Pathological effects of parathion (16 mg/kg) on the spleen were reported in C57Bl/6 mice; a significant decrease in spleen weight was observed 2 days after a single oral dose (Casale et al., 1983). Long-term studies conducted by the United States National Toxicology Program did not find increases in non-neoplastic pathology in the spleen or bone marrow of mice or rats treated with parathion for up to 2 years (NTP, 1979). No effect on spleen weight was observed in a study in BALB/c mice given daily intraperitoneal injections of paraoxon at doses of 30 or 40 nmol for 6 weeks (Fernandez-Cabezudo et al., 2008).

Immunosuppressive effects of parathion in mice were first reported by Wiltrout et al. (1978). Subsequent studies of hypersensitivity demonstrated that exposure of mice to parathion led to the following effects in response to immunogenic challenge with picryl chloride: increases in the severity of dermatitis, serum IgE and IgG2a levels, numbers of helper T-cells and IgE-positive B-cells, production of Th1 and Th2 cytokines, and production of IgE in auricular lymph-node cells; and a marked decrease in numbers of splenic regulatory T-cells (Fukuyama et al., 2012). Another study by the same group showed that pretreatment with parathion before allergic challenge in mice caused a marked increase in numbers of helper and cytotoxic T-cells, and levels of Th1 and Th2 cytokines (Fukuyama et al., 2011). Altered host resistance to viral (Selgrade et al., 1984) and bacterial (Fernandez-Cabezudo et al., 2010) infections upon exposure to parathion or paraoxon has also been reported in mice.

Suppression of the humoral immune response by parathion has been reported in studies in mice. Numbers of IgM plaque-forming cells were reduced by 65% in C57Bl/6 mice given parathion (16 mg/kg, per os) 2 days after immunization with sheep erythrocytes (Casale et al., 1984); however, the immunosuppressive dose also caused signs of cholinergic poisoning and 20% mortality. Non-poisonous doses of parathion (4 mg/kg, per os) had no effect on markers of humoral immunity. Effects on the cell-mediated immune system were demonstrated in studies of exposure to parathion in mice. In C57Bl/6 mice treated with parathion (4 mg/kg, per os) for 14 days, leukocyte counts were elevated on days 2 and 5, and effects on haematopoietic stem cells in the bone marrow were also observed (Gallicchio et al., 1987a). In a study of ovalbumin-induced allergic immune response in mice, oral exposure to parathion led to marked increases in serum IgE levels, the number of IgE-positive B cells, and

also levels of IgE and cytokines in lymph nodes, and eosinophils and chemokines in broncho-alveolar lavage fluid, and interleukin IL-10 and IL-17A in the lung (Nishino et al., 2013). Similar effects were observed in studies in guinea-pigs. Ovalbumin sensitization of guinea-pigs increased the vulnerability to parathion-induced airway hyper-reactivity (Proskocil et al., 2008, 2013).

In vitro

Casale et al. (1993) found that exposure of mouse T-cell lymphoma lines CTLL2 to paraoxon produced marked concentration-dependent inhibition of interleukin IL2-driven cell proliferation.

4.2.4 Cell proliferation and death

(a) Humans

No data from exposed humans were available to the Working Group.

The Working Group identified several studies examining effects of parathion on MCF-10F cells, a breast epithelial cell line spontaneously immortalized from non-malignant cells. In the first study, proliferation was increased in MCF-10F cells treated with parathion at 100 ng/mL, when compared with controls (Calaf & Roy, 2007a). Expression of the following proteins was enhanced in treated cells: EGFR, NOTCH-4, DVL-2, EZRIN, RAC 3, RHO-A, trio, c-kit, β catenin, and mutant p53. This increase in expression was significantly inhibited by atropine. Purified mRNAs from treated cells were used to synthesize cDNA probes, which were then studied in a human cell-cycle array of 96 genes (GE Assay Q Series Human DNA cell cycle cDNA expression array membranes). Treatment with parathion was associated with the elevated expression of 12 genes, including cyclins and cyclin-dependent kinases. In a second study with the same design, Calaf & Roy (2008a) studied the effect of parathion on a human cell-cycle array of 96 genes involved in cell proliferation and metastasis (Human Cancer Microarray by SuperArray). Parathion modulated the expression of 44 of the 96 genes involved in cell proliferation, including insulin-like growth factor binding proteins (IGFBP), cyclins, and cyclin-dependent kinase 4. In a third similar study, Calaf & Roy (2008b) found increased protein expression of NOTCH-4, DVL-2, CD146 and β catenin, also indicative of cell proliferation and adhesion potential.

In a study on the apoptotic effects of parathion and other chemicals on the human acute T-cell leukaemia cell line J45.01, parathion (0.03, 0.1, and 0.3 μM) caused a dose-dependent decrease in the percentage of viable cells and increased the percentage of apoptotic cells after 4 and 8 hours (Fukuyama et al., 2010). Co-incubation with the caspase inhibitor Z-VAD-fmk (tested on cells receiving parathion at 0.3 μM) was protective, while the caspase-3 inhibitor Ac-DEVD-CHO was not. There was a dose-dependent increase in the proportion of caspase 3/7 (but not caspase-8 or 9) activity, and in levels of DNA fragmentation, which was blocked by one or more of the caspase inhibitors.

Erythrocyte and granulocyte–macrophage progenitor cells, cloned from human bone marrow taken from healthy volunteers or heart surgery patients, were exposed to paraoxon (Gallicchio et al., 1987b). Erythroid as well as granulocyte colony formation and burst-forming erythroid units were inhibited in a strongly dose-dependent fashion, with sensitivity as low as 0.001 μM for burst erythroid and granulocyte colony formation.

Paraoxon or parathion at 1 mM induced time-dependent increases in apoptosis in human neuroblastoma cells (Carlson et al., 2000). Cyclosporin A, an inhibitor of the mitochondrial permeability transition pore, was protective. Paraoxon (1 mM) and parathion (100 μM, 1 mM) induced significant time-dependent increases in caspase-3 activation, which was modulated by pretreatment with cyclosporin

A. In a study on non-cholinergic neurotoxic effects, neuroblastoma cells exposed to paraoxon showed two upregulated genes (one of which was thyroid hormone receptor-associated protein 5), and thirteen downregulated genes, four (*APC*, *FAS*, *MDM4,* and *PTEN*) of which are involved in cell proliferation or apoptosis regulation (Qian et al., 2007). Pomeroy-Black & Ehrich (2012) also found that paraoxon upregulated the mitogen-activated protein kinase (MAPK) pathway in SY5Y cells, and caused significant activation of protein kinase B (Akt) in the phosphatidylinositol PI3K cell-survival pathway.

(b) Experimental systems

(i) In vivo

Cabello et al. (2001) investigated the impact on the structure of the mammary gland of subacute exposure to parathion (2500 µg/kg bw, subcutaneous injection, twice per day for 5 days) in Sprague Dawley rats (age 16 days or 39 days). The rats were killed 16 hours after the last injection. In whole mounts of mammary glands from the left side of rats exposed from age 21 days, parathion had no effect on terminal end bud or alveolar bud density. In rats exposed from age 39 days (normally a period of active differentiation of terminal end buds into alveolar buds), the density of terminal end buds was markedly increased compared with control animals (terminal end bud density, 12.04 ± 1.77/mm^2 versus 3.30 ± 0.27/mm^2), and a markedly lower density of alveolar buds (alveolar bud density, 1.28 ± 0.52/mm^2 versus 20.80 ± 1.68/mm^2). Histological examination of mammary glands excised from the right side showed a significant ($P < 0.05$) increase in the size of terminal end buds and the number of epithelial layers.

The apoptotic effect of parathion on sperm was studied in young mice (onset of spermatogenesis) and in adult mice (full spermatogenesis) (Bustos-Obregón et al., 2001). Parathion increased the proportion of cells undergoing apoptosis in young animals and adults, affecting spermatocytes at the beginning of the meiotic process, and spermatids at the elongation period.

(ii) In vitro

In the study by Fukuyama et al. (2010) in primary mouse thymocytes discussed above, parathion had a strong adverse, dose-dependent, effect on cell viability, and increased the proportion of cells undergoing apoptosis. Caspase 3/7 (but not caspase 8 or 9) activity was increased by parathion, and reduced by caspase 3/7 inhibitors (Z-VAD-fmk and Ac-DEVD-CHO) in these cells. Neither caspase-3/7 inhibitor had any significant measurable effect on cell viability, but Z-VAD-fmk reduced the proportion of apoptotic mouse thymocytes affected by parathion.

Paraoxon (0.001–0.01 µM) increased the activity of caspase-3 and induced apoptosis in a concentration-dependent manner in the mouse lymphocytic leukaemia T-cell line, EL4 (Saleh et al., 2003a). Parathion had a similar effect, but at higher concentrations of 0.05–10 µM. In a follow-up study, a caspase-9 inhibitor (zLEHD-fmk) attenuated apoptosis, and blocked the activation of caspases 3, 8, and 9 by paraoxon, implicating caspase 9-dependent mitochondrial pathways in paraoxon-induced apoptosis (Saleh et al., 2003b). In EL4 T-cells, Li et al. (2010) demonstrated attenuation of parathion-induced apoptosis, and inhibition of paraoxon-induced increased expression of caspase-12, by calcium-channel receptor antagonists or by calcium chelation.

Seminiferous tubules harvested from CF1 mice (age, 90 days) exposed to parathion or paraoxon (0.8 mM) showed a substantial reduction in cell replication, compared with controls (Rodriguez & Bustos Obregon, 2000; Rodriguez et al., 2006).

Paraoxon induced apoptosis and inhibited cell replication in a neuronal cell line, differentiated PC12 cells derived from rat adrenal medulla pheochromocytoma, in several studies (Flaskos

et al., 1994; Slotkin et al., 2007; Sadri et al., 2010). In hippocampal cells harvested from Wistar rat neonates, paraoxon reduced cell viability (Yousefpour et al., 2006). Neurotoxicity and activation of rat primary glial cells in response to exposure to parathion in vitro has also been demonstrated (Zurich et al., 2004).

A positive association between exposure to parathion and cytotoxicity was reported in a fish-derived cell line FG-9307 (Li & Zhang, 2001).

4.2.5 Other mechanisms

Calaf & Roy (2007b) studied the effects of parathion on cell transformation and gene expression in the immortalized human breast epithelial cells MCF-10F. Cells treated with parathion (100 ng/mL) exhibited anchorage-independent growth and invasiveness, measured 20 passages after treatment. Protein expression in treated cells was enhanced for mutant p53 protein, and other proteins that play a role in the cell cycle (see Section 4.2.4).

In a genome-wide DNA methylation study in a human haematopoietic cell line derived from erythroblastic leukaemia (K562), parathion elevated the methylation of gene-promoter CpG sites, including for genes involved in cell differentiation, DNA dealkylation involved in DNA repair, and regulation of apoptosis and cell proliferation (Zhang et al., 2012).

4.3 Data relevant to comparisons across agents and end-points

4.3.1 General description of the database

The analysis of the in-vitro bioactivity of the agents reviewed in *IARC Monographs* Volume 112 (i.e. malathion, parathion, diazinon, and tetrachlorvinphos) was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast™) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013). At its meeting in 2014, the Advisory Group to the *IARC Monographs* programme encouraged inclusion of analysis of high-throughput and high-content data (including from curated government databases) (Straif et al., 2014).

Diazinon, malathion, and parathion, as well as the oxon metabolites, malaoxon and diazoxon, are among the approximately 1000 chemicals tested across the full assay battery of the Tox21 and ToxCast research programmes as of 3 March 2015. This assay battery includes 342 assays, for which data on 821 assay end-points are publicly available on the website of the ToxCast research programme (EPA, 2016a). *Z*-Tetrachlorvinphos (CAS No. 22248-79-9; a structural isomer of tetrachlorvinphos), and the oxon metabolite of parathion, paraoxon, are among an additional 800 chemicals tested as part of an endocrine profiling effort using a subset of these assays. Glyphosate was not tested in any of the assays carried out by the Tox21 or ToxCast research programmes.

Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is also publicly available (EPA, 2016b). It should be noted that the metabolic capacity of the cell-based assays is variable, and generally limited. [The Working Group noted that the limited activity of the oxon metabolites in in-vitro systems may be attributed to the high reactivity and short half-life of these compounds, hindering interpretation of the results of in-vitro assays.]

4.3.2 Aligning in-vitro assays to 10 "key characteristics" of known human carcinogens

In order to explore the bioactivity profiles of the compounds under evaluation in *IARC Monographs* Volume 112 with respect to their potential impact on mechanisms of

carcinogenesis, the Working Group first mapped the 821 available assay end-points in the Tox21/ToxCast database to the key characteristics of known human carcinogens (IARC, 2014). Independent assignments were made by the Working Group members and *IARC Monographs* staff for each assay type to the one or more "key characteristics." The assignment was based on the biological target being probed by each assay. The consensus assignments comprise 263 assay end-points that mapped to 7 of the 10 "key characteristics" as shown below.

1. *Is electrophilic or can undergo metabolic activation (31 end-points)*: the 31 assay end-points that were mapped to this characteristic measure cytochrome p450 (CYP) inhibition (29 end-points) and aromatase inhibition (2 end-points). All 29 assays for CYP inhibition are cell-free. These assay end-points are not direct measures of electrophilicity or metabolic activation.
2. *Is genotoxic (9 end-points):* the only assay end-points that mapped to this characteristic measure TP53 activity. [The Working Group noted that while these assays are not direct measures of genotoxicity, they are an indicator of DNA damage.]
3. *Alters DNA repair or causes genomic instability (0 end-points)*: no assay end-points were mapped to this characteristic.
4. *Induces epigenetic alterations (11 end-points):* assay end-points mapped to this characteristic measure targets associated with DNA binding (4 end-points) and histone modification (7 end-points) (e.g. histone deacetylase).
5. *Induces oxidative stress (18 end-points):* a diverse collection of assay end-points measure oxidative stress via cell imaging, and markers of oxidative stress (e.g. nuclear factor erythroid 2-related factor, NRF2). The 18 assay end-points that were mapped to this characteristic are in subcategories relating to metalloproteinase activity (5), oxidative stress (7), and oxidative-stress markers (6).
6. *Induces chronic inflammation (45 end-points)*: the assay end-points that were mapped to this characteristic include inflammatory markers and are in subcategories of cell adhesion (14), cytokines (e.g. interleukin 8, IL8) (29), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity (2).
7. *Is immunosuppressive (0 end-points):* no assay end-points were mapped to this characteristic.
8. *Modulates receptor-mediated effects (81 end-points):* a large and diverse collection of cell-free and cell-based nuclear and other receptor assays were mapped to this characteristic. The 81 assay end-points that were mapped to this characteristic are in subcategories of AhR (2), androgen receptor (11), estrogen receptor (18), farnesoid X receptor (FXR) (7), others (18), peroxisome proliferator-activated receptor (PPAR) (12), pregnane X receptor_vitamin D receptor (PXR_VDR) (7), and retinoic acid receptor (RAR) (6).
9. *Causes immortalization (0 end-points):* no assay end-points were mapped to this characteristic.
10. *Alters cell proliferation, cell death, or nutrient supply (68 end-points):* a collection of assay end-points was mapped to this characteristic in subcategories of cell cycle (16), cytotoxicity (41), mitochondrial toxicity (7), and cell proliferation (4).

Assay end-points were matched to a "key characteristic" in order to provide additional insights into the bioactivity profile of each chemical under evaluation with respect to their potential to interact with, or have an effect on, targets that may be associated with carcinogenesis. In addition, for each chemical, the results of the in-vitro assays that represent each "key characteristic" can be compared with the results for a larger compendium of substances with similar in-vitro data, so that particular chemical can be

aligned with other chemicals with similar toxicological effects.

The Working Group then determined whether a chemical was "active" or "inactive" for each of the selected assay end-points. The decisions of the Working Group were based on raw data on the concentration–response relationship in the ToxCast database, using methods published previously (Sipes et al., 2013) and available online (EPA, 2016b). In the analysis by the Working Group, each "active" was given a value of 1, and each "inactive" was given a value of 0.

Next, to integrate the data across individual assay end-points into the cumulative score for each "key characteristic," the toxicological prioritization index (ToxPi) approach (Reif et al., 2010) and associated software (Reif et al., 2013) were used. In the Working Group's analyses, the ToxPi score provides a measure of the potential for a chemical to be associated with a "key characteristic" relative to 178 other chemicals that have been previously evaluated in the *IARC Monographs* and that had been screened by ToxCast. Assay end-point data were available in ToxCast for these 178 chemicals, and not for other chemicals previously evaluated by *IARC Monographs*. ToxPi is a dimensionless index score that integrates of multiple different assay results and displays them visually. The overall score for a chemical takes into account score for all other chemicals in the analysis. Different data are translated into ToxPi scores to derive slice-wise scores for all compounds as detailed below, and in the publications describing the approach and the associated software package (Reif et al., 2013). Within the individual slice, the values are normalized from 0 to 1 based on the range of responses across all chemicals that were included in the analysis by the Working Group.

The list of ToxCast/Tox21 assay end-points included in the analysis by the Working Group, description of the target and/or model system for each end-point (e.g. cell type, species, detection technology, etc.), their mapping to 7 of the 10 "key characteristics" of known human carcinogens, and the decision as to whether each chemical was "active" or "inactive" are available as supplemental material to Volume 112 (see Annex I) The output files generated for each "key characteristic" are also provided in the supplemental material, and can be opened using ToxPi software that is freely available for download without a licence (Reif et al., 2013).

4.3.3 Specific effects across 7 of the 10 "key characteristics" based on data from high-throughput screening in vitro

The relative effects of parathion and paraoxon were compared with those of 178 chemicals selected from the more than 800 chemicals previously evaluated by the *IARC Monographs* and also screened by the ToxCast/Tox21 programmes, and with the other three compounds evaluated in the present volume of the *IARC Monographs* (Volume 112) and their metabolites. Of these 178 chemicals previously evaluated by the *IARC Monographs* and screened in the ToxCast/Tox21 programmes, 8 are classified in Group 1 (*carcinogenic to humans*), 16 are in Group 2A (*probably carcinogenic to humans*), 58 are in Group 2B (*possibly carcinogenic to humans)*, 95 are in Group 3 (*not classifiable as to its carcinogenicity to humans*), and 1 is in Group 4 (*probably not carcinogenic to humans).* The results are presented as a rank order of all compounds in the analysis arranged in the order of their relative effect. The relative positions of parathion and paraoxon in the ranked list are also shown on the *y* axis. The inset in the scatter plot shows the components of the ToxPi chart as subcategories that comprise assay end-points in each characteristic, as well as their respective colour-coding. On the top part of the graph on the right-hand side, the two highest-ranked chemicals in each analysis are shown to represent the maximum ToxPi scores (with the scores in parentheses). At the bottom of the right-hand side, ToxPi images and scores

(in parentheses) for parathion and paraoxon are shown.

Characteristic (1) *Is electrophilic or can undergo metabolic activation:* Parathion was tested for all 31 end-points. It was active in 18 of the 29 CYP-inhibition assay end-points (all cell-free). The highest ranked of the 178 chemicals included in the comparison was malathion, which was active for 20 out of 29 assay end-points. Parathion was inactive for the two aromatase-inhibition assay end-points. Paraoxon was only tested for the two aromatase-inhibition assay end-points and was active for both (Fig. 4.4).

Characteristic (2) *Is genotoxic*: Parathion and paraoxon were tested and found inactive in 9 and 6, respectively, of the 9 available TP53 assay end-points. In comparison, top-ranked chemicals chlorobenzilate and clomiphene citrate were found to be active for 7 out of the 9 assay end-points for which they were tested (Fig. 4.5).

Characteristic (4) *Induces epigenetic alterations:* Parathion paraoxon were tested and found inactive in 11 and 4, respectively, of the 11 available assay end-points. In comparison, the highest-ranked chemical *Z*-tetrachlorvinphos was active in all 4 of the DNA binding assay end-points, but was not tested in any of the 7 transformation-assay end-points (Fig. 4.6).

Characteristic (5) *Induces oxidative stress*: Parathion was tested in all 18 assays, and was active in 2 out of the 6 oxidative-stress marker assay end-points. Paraoxon was inactive for the 7 assay end-points for which it was tested. In comparison to the two highest-ranked chemicals, carbaryl and tannic acid, parathion was moderately active in assays with metalloproteinases and oxidative-stress markers. The metalloproteinase assay end-points were highly selective with the maximal responder (i.e. carbaryl) only activating 2 out of 5 end-points. Parathion displayed activity in a single assay (BSK_hDFCGF_MMP1_up). Parathion also induced transcription-factor activation of NRF2 and the metal response element (MRE) (Fig. 4.7).

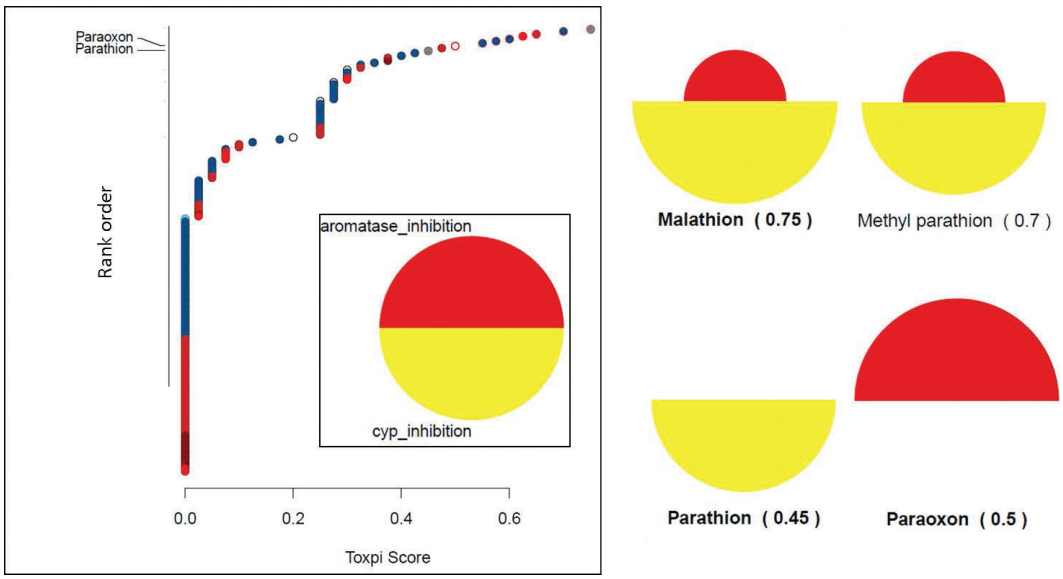
Characteristic (6) *Induces chronic inflammation*: Parathion was tested for all 45 assay-end-points, while paraoxon was tested for 2 (both NFkB); both chemicals showed weak to no activity across assay end-points associated with chronic inflammation when compared with the highest-ranked compounds 4,4′-methylenedianiline and malaoxon (Fig. 4.8).

Characteristic (8) *Modulates receptor-mediated effects:* Parathion and paraoxon were tested for all 81 assay end-points in this group. In comparison to the two highest-ranked chemicals, clomiphene citrate and kepone, parathion selectively activated both AhR assay end-points. In addition, parathion showed appreciable activity in 14 "other nuclear receptor" assay end-points, making it one of the most highly active chemicals overall. Paraoxon showed relatively weak receptor activity (Fig. 4.9).

Characteristic (10) *Alters cell proliferation, cell death, or nutrient supply:* Parathion and paraoxon were tested in 67 and 27, respectively, of the 68 assay end-points, but showed almost no activity for end-points associated with cytotoxicity or cellular proliferation (Fig. 4.10).

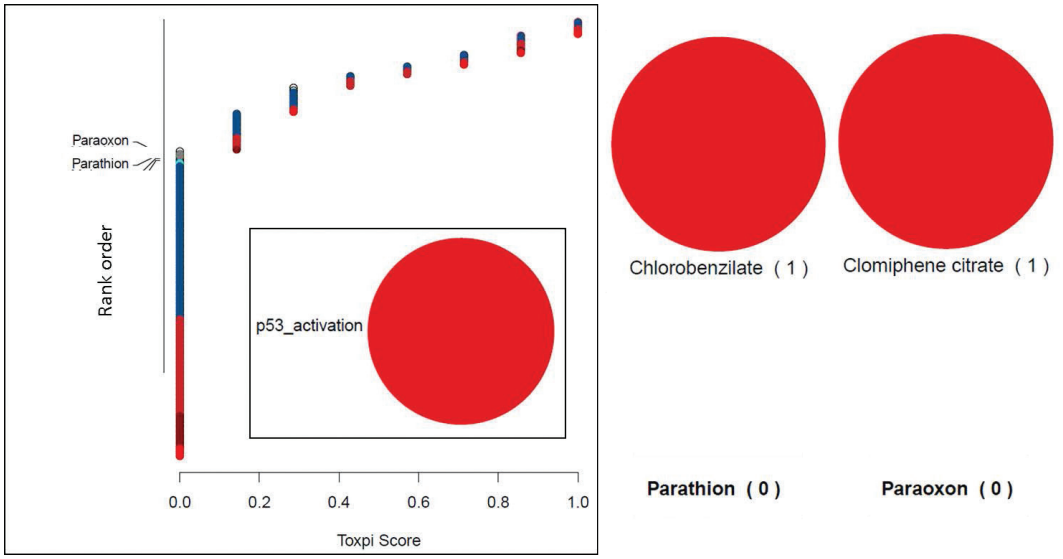
Overall, parathion was active in 42 out of 263 assay end-points for which it was tested. The analysis of the ToxCast/Tox21 data for parathion corroborates findings in other model systems as described in Section 4.2. Its oxon metabolite, paraoxon, showed little bioactivity under the conditions of these assay end-points, with activity for only 7 assay end-points of the 137 tested. The limited activity of paraoxon may be attributed to the high reactivity and short half-life of this

Fig. 4.4 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to enzyme inhibition



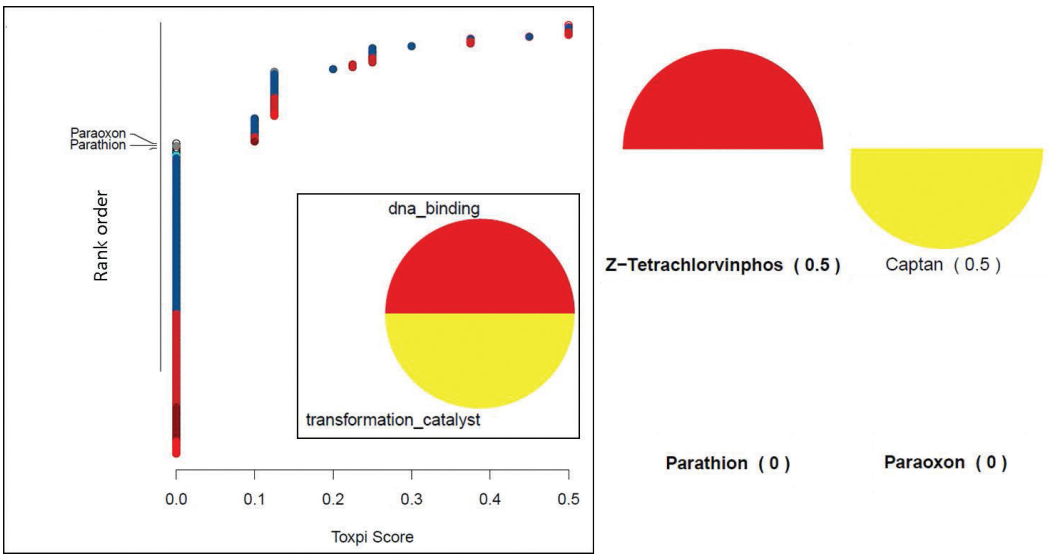
On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, malathion and methyl parathion) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

Fig. 4.5 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to genotoxicity



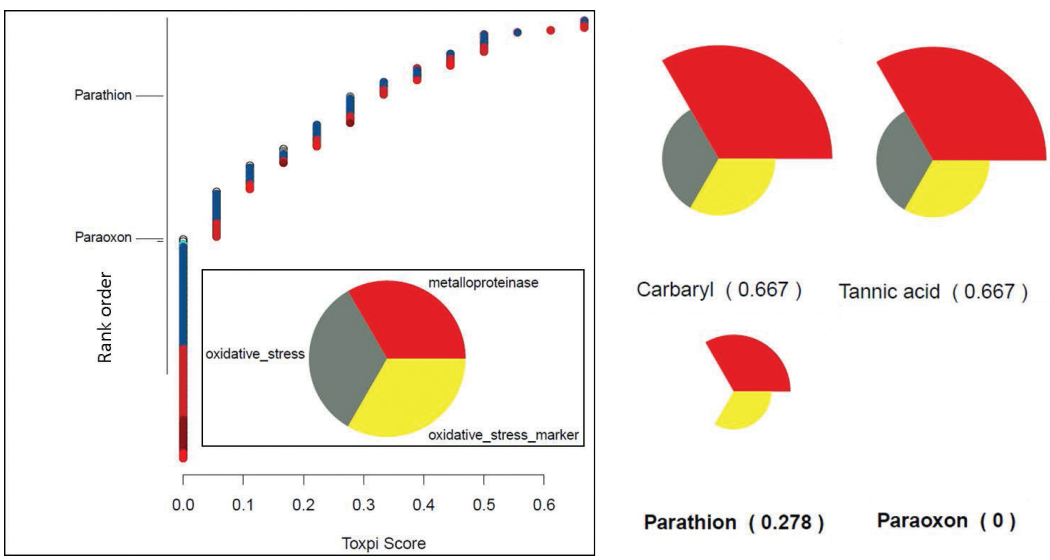
On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, chlorobenzilate and clomiphene citrate) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

Fig. 4.6 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to epigenetic alterations



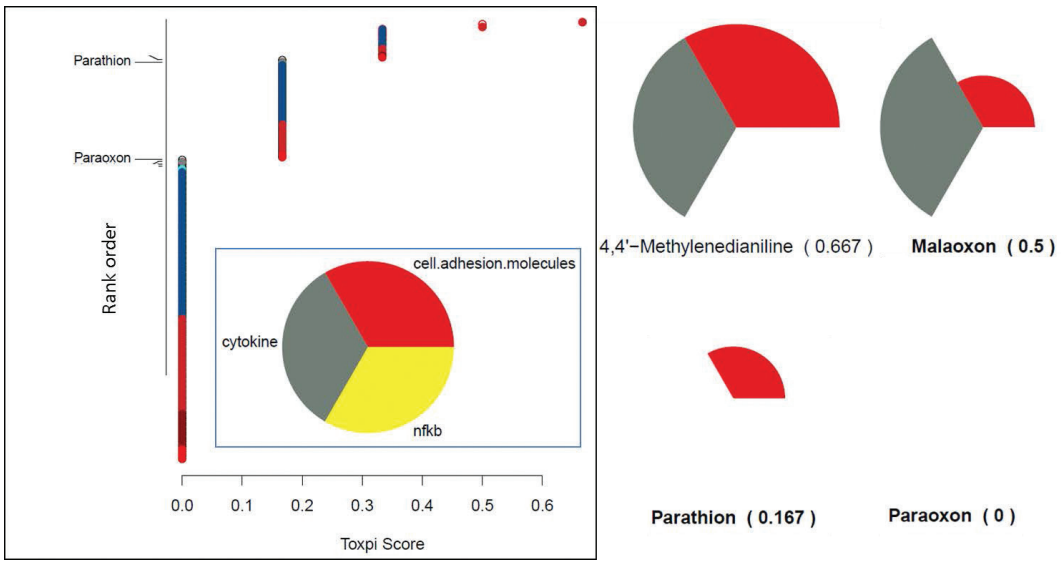
On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, Z-tetrachlorvinphos and captan) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

Fig. 4.7 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to oxidative stress



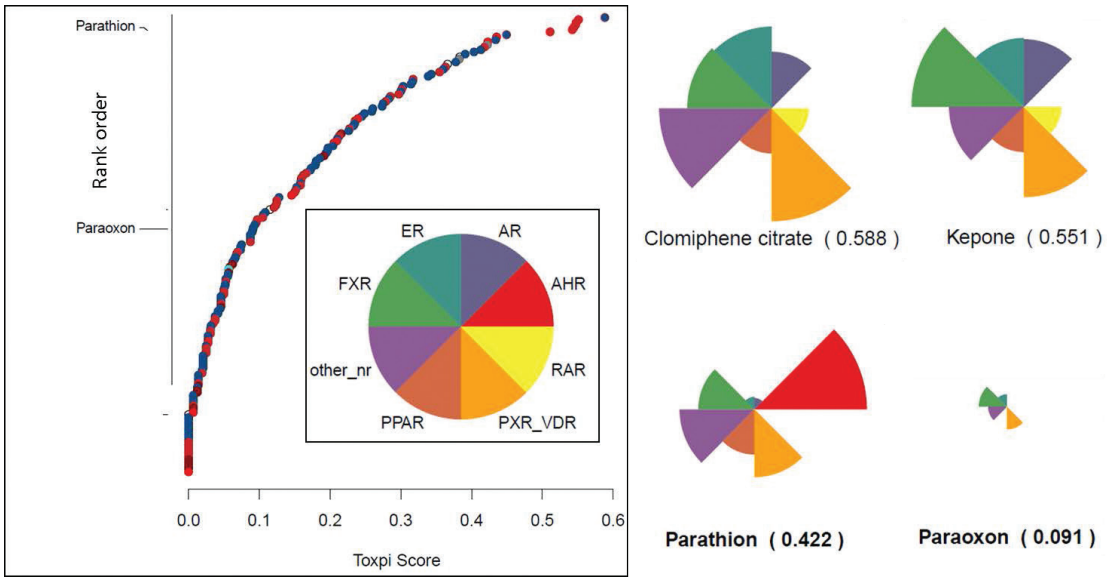
On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, carbaryl and tannic acid) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

Fig. 4.8 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to chronic inflammation



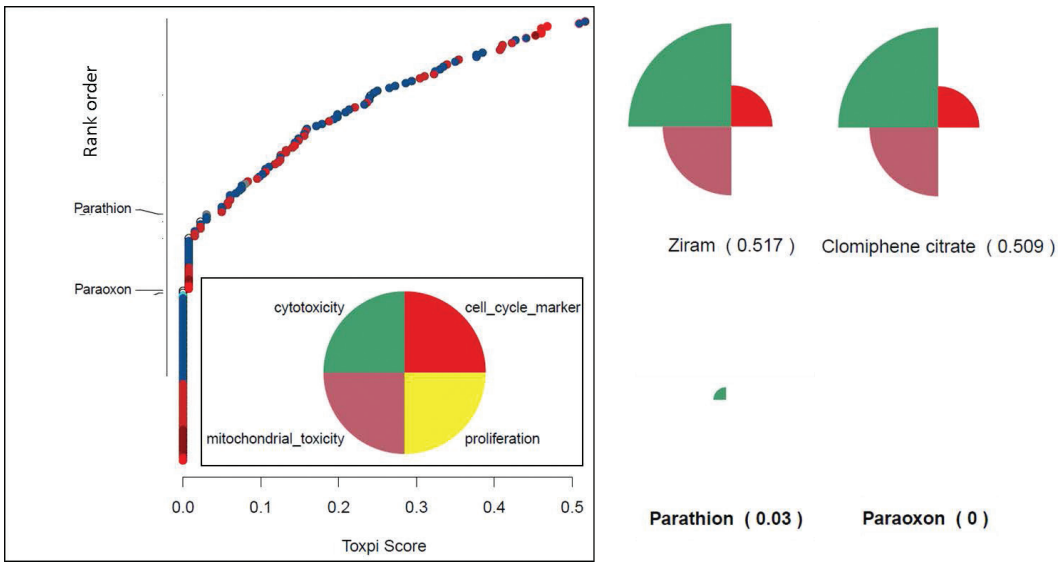
On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, 4,4′-methylenedianiline and malaoxon) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

Fig. 4.9 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to receptor-mediated effects



On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, clomiphene citrate and kepone) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

Fig. 4.10 ToxPi ranking for parathion and its metabolite paraoxon using ToxCast assay end-points mapped to cytotoxicity and cell proliferation



On the left-hand side, the relative ranks of parathion, and its metabolite paraoxon, are shown (*y*-axis) with respect to their toxicological prioritization index (ToxPi) score (*x*-axis) compared with the other chemicals evaluated in the present volume (*IARC Monographs* 112) and with 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the two highest-ranked chemicals (in this case, clomiphene citrate and ziram) and the target chemicals (parathion and paraoxon) are shown with their respective ToxPi score in parentheses.

compound, which hampers interpretation of the results of the in-vitro assay end-points.

4.4 Susceptibility

A nested case–control study of Caucasian pesticide applicators within the AHS examined the interactions between exposure to 41 pesticides and 152 single-nucleotide polymorphisms (SNP) in nine genes involved in the vitamin D pathway among 776 cases of cancer of the prostate and 1444 controls (Karami et al., 2013; see Section 2.2.1). The strongest interaction observed in this study was between the *RXRB* (Retinoid-X-Receptor β) gene variant rs1547387 and parathion exposure. In addition, significant interactions were observed between *GC* (Group specific Component vitamin D-binding protein) gene variants rs7041 and rs222040, prostate cancer, and use of parathion.

Paraoxonase 1 (PON1) is an enzyme involved in metabolism of parathion and other organophosphate pesticides (see Section 4.1). It is a polymorphic enzyme, and several well-established common genetic variants that markedly affect its activity and protein levels have been identified in humans (Humbert et al., 1993; Costa et al., 2013). No study has examined cancer outcomes as a function of PON1 polymorphism. Two studies (Lee et al., 2003; Singh et al., 2011a) were conducted in populations of agricultural workers who were exposed to uncharacterized mixtures of pesticides, and demonstrated a significant association between *PON1* polymorphisms (*PON1* 192QQ) and markers of genotoxicity (DNA damage measured by comet assay in circulated lymphocytes). The follow-up studies in some of these populations demonstrated that genetic variants in several other enzymes involved in metabolism such as CYP2D6, CYP2D9, GSTM1, and NAT2 also had a significant effect on markers for

genotoxicity (DNA damage) (Singh et al., 2011b, 2012). One study found a significant association between exposure to organophosphates (not exclusive to parathion), sperm quality parameters, and *PON1* 192RR genotype (Pérez-Herrera et al., 2008).

The greater sensitivity of weanling rodents of either sex and of adult females, compared with adult males, to acute toxicity of parathion (Gagné & Brodeur, 1972; Harbison, 1975; Deskin et al., 1978) is attributed to age- and sex-related differences in the toxicokinetics of the parent compound and its metabolites. Embryo and fetus lethality in studies was seen in rats exposed to parathion during gestation, in the absence of severe maternal toxicity (Harbison, 1975). Other studies of neonatal exposure to parathion indicated that female rats were more sensitive than male rats to the later alterations in response to high-fat diet in adulthood (Lassiter et al., 2008; Slotkin, 2011).

4.5 Other adverse effects

4.5.1 Humans

Although currently unusual in industrialized countries such as the USA, toxicity caused by exposure to parathion is a common source of severe poisoning in low- and middle-income countries (Rumack, 2015). Epidemiological evidence, including evidence of hospitalization and death due to accidental dermal exposure and ingestion, indicates that parathion is more toxic to children than to adults (Hayes & Laws, 1991). In several studies of exposure in humans, parathion was shown to be an inhibitor of erythrocyte and plasma cholinesterase activity (NIOSH, 1976). Acute and long-term exposure to parathion have been associated with various clinical signs including nausea, vomiting, abdominal cramps, diarrhoea, excessive salivation, headache, weakness, difficulty in breathing, vision impairment, convulsions, central nervous system depression, paralysis, coma, and respiratory failure (IARC, 1983; O'Neil et al., 2013).

4.5.2 Experimental systems

In numerous studies, parathion induced cholinergic effects, including inhibition of plasma, erythrocyte, and brain cholinesterase activity at doses as low as 0.0024 mg/kg bw per day, and corresponding clinical signs (abnormal gait, tremors, and reduced activity) at doses as low as 1.75 mg/kg bw per day (EPA, 1986b, c, 1991b; Atkinson et al., 1994). In the 2-year study of toxicity and carcinogenicity in female rats, the inhibition of cholinesterase activity was accompanied by clinical signs including tremors, abnormal gait, and increased mortality (EPA, 1984, 1986b).

Other effects in long-term studies were decreased body-weight gain in rats (EPA, 1986c). Effects on the eye were also reported in the combined study of chronic toxicity and carcinogenicity in rats. Parathion induced gross retinal abnormalities in males and females, in addition to cataracts and turbid lenses in females, and epithelium, optic nerve, and ciliary body degeneration, as well as retinal atrophy in males (EPA, 1984, 1986b, c).

A study of developmental neurotoxicity reported reductions in motor activity, and in the density of muscarinic receptor binding in the cerebral cortex (Stamper et al., 1988). In another study of developmental neurotoxicity in rats given parathion at a dose of 0.1 or 0.2 mg/kg per day on postnatal days 1–4, learning and memory impairment when tested with a maze and decreased reflexes were observed in males and females at the highest dose (Timofeeva et al., 2008).

5. Summary of Data Reported

5.1 Exposure data

Parathion is a broad-spectrum organophosphate insecticide that is effective against a wide range of insects on crops. It was first used in 1947, but because of its toxicity to wildlife and human health, use of parathion has been banned or severely restricted throughout the world. Most countries banned parathion in the 1980s and 1990s, and all authorizations for use in the European Union and USA were banned by 2003. Most exposure to workers is via the dermal route in both manufacturing and use of parathion. Exposure can vary considerably depending on the task, the method of application, the environmental conditions, the rate of application, and the operator technique. The available data indicated that general population exposures to parathion are low subsequent to restrictions on its use.

5.2 Human carcinogenicity data

In its evaluation of the epidemiological data on parathion, the Working Group identified reports from two cohort studies, plus two additional case–control studies, all in the USA or Canada. The Agricultural Health Study (AHS) is the major source of evidence from cohort studies, with reports on non-Hodgkin lymphoma (NHL), melanoma, and cancers of the prostate, breast, and colorectum. The Florida pest-control worker cohort reported on a nested case–control study of cancer of the lung. Case–control studies were also reported on NHL and cancer of the prostate. The Working Group observed that evidence regarding parathion remains sparse, that several studies reported elevated odds ratios that did not reach statistical significance, and the few associations that have been detected have not been replicated in separate studies.

5.2.1 Non-Hodgkin lymphoma

The relationship between exposure to parathion and NHL was examined in two studies. The case–control report was from the pooled analysis of three case–control studies of farmers in the mid-western USA, and yielded a multivariable-adjusted (but not for other pesticides) odds ratio (OR) of 2.9 (95% CI, 0.9–9.7). In a recent report from the AHS, there was no association between parathion and NHL; the relative risk of ever having used parathion was 1.1 (95% CI, 0.8–1.4), and there was no evidence of heterogeneity across histological subtypes, or a trend with increasing number of days of use. The Working Group noted the inconsistency of these results and concluded that there was no strong evidence of an association between exposure to parathion and NHL.

5.2.2 Cancer of the prostate

Three publications reported on the relationship between exposure to parathion and cancer of the prostate. The first was a case–control study in Canada that estimated exposure to parathion from a locally derived job-exposure matrix (OR for ever use, 1.51; 95% CI, 0.94–2.41) and there was a suggestion of trend (P = 0.06) with lifetime-days of parathion use. From the AHS, two nested case–control studies have been reported, with a large study that included 1962 cases finding that overall there was no significant association or trend across quartiles of cumulative lifetime exposure; however, when restricted to aggressive tumours of the prostate, risk was elevated (OR, 1.96; 95% CI, 1.10–3.50) in the subset with the lowest quartile of exposure. A further analysis of cancer of the prostate in the AHS was in a nested case–control study that included a smaller number of subjects (e.g. there were 776 cases of cancer of the prostate) for whom biospecimens were available for genetic analysis. Overall, there was no association with ever having used

parathion (OR, 1.02; 95% CI, 0.78–1.33); however, effect modification was detected such that significant elevations in risk were seen in subgroups defined by the presence of variants in two vitamin-D pathway genes. The Working Group noted that while there is no consistent evidence of an association with cancer of the prostate overall, recent results from a large and comprehensive cohort study have revealed possible increases in risk for subgroups defined on the basis of variation in vitamin-D pathway genes.

5.2.3 Melanoma

A statistically significant association between parathion and cutaneous melanoma was detected in a single case–control study nested within the AHS (OR for any use, 1.9; 95% CI, 1.2–3.0). There was also a statistically significant monotonic trend in increasing risk with more frequent use, and a plausible effect modification among those who also applied lead arsenate; users of parathion who were exposed to lead arsenate had a much higher risk of developing melanoma than those who were not exposed to lead arsenate. The Working Group recognized that there may be residual confounding with established risk factors for melanoma, and noted the lack of replication in other settings.

5.2.4 Other cancer sites

A single report from the AHS examined risk of cancer of the breast among women, and although there was no significant relationship overall with whether husbands used parathion (RR, 1.3; 95% CI, 0.8–2.1), significantly increased risk was seen for those who had a family history of breast cancer, and for those who lived in one of the two states investigated. Also within the AHS, a study on cancer of the colorectum found that it was not associated with parathion use. Finally, the single study that assessed cancer of the lung also reported a non-significant increase in risk but owing to its limitations, this study did not contribute substantially to the conclusions of the Working Group.

5.3 Animal carcinogenicity data

Parathion was tested for carcinogenicity in male and female mice in two feeding studies, in male and female rats in five feeding studies, and in female rats in one study with subcutaneous injection.

In one feeding study in mice, parathion produced a significant increase in the incidence of bronchiolo-alveolar adenoma, and bronchiolo-alveolar adenoma or carcinoma (combined) in treated males. In treated females, there was an increase in the incidence of malignant lymphoma. In the other feeding study, there was no significant increase in tumour incidence in male or female treated mice.

In a first feeding study in rats, there was a significant increase in the incidence of adrenal cortical adenoma, adrenal cortical adenoma or carcinoma (combined), thyroid follicular cell adenoma, and pancreatic islet cell carcinoma in treated males. Also significant was the increase in the incidence of adrenal cortical adenoma, adrenal cortical adenoma or carcinoma (combined), and mammary gland fibroadenoma observed in treated females. In a second feeding study, a significant increase in the incidence of pancreatic exocrine adenoma, exocrine adenoma or carcinoma (combined), and islet cell adenoma was observed in treated males only. In a third feeding study, parathion non-significantly increased the incidence of follicular cell adenoma of the thyroid gland in males only. The two other feeding studies with parathion gave negative results. In the study with parathion given by subcutaneous injection, there was a significant increase in the incidence of adenocarcinoma of the mammary gland in female rats.

5.4 Mechanistic and other relevant data

Rapid absorption of parathion from the gastrointestinal tract occurs in humans and experimental species, but dermal absorption is less efficient. Data are limited on how much compound is absorbed through inhalation in humans and experimental animals. Parathion is rapidly distributed in the blood after absorption in humans; however, no data on distribution to other tissues in humans were available. Most (94–99%) of the absorbed parathion is bound to proteins, mostly serum albumin, in the blood. After absorption in rats, parathion is readily taken up by liver, kidney, and fat.

The metabolism of parathion is similar in humans and experimental species. The bioactive metabolite, paraoxon, is formed via cytochrome P450 (CYP)-catalysed oxidation, and is then degraded by carboxylesterase and paraoxonase 1, liberating *para*-nitrophenol. Dearylation of parathion is another pathway catalysed by CYP. In humans, the major pathway of oxidation for parathion is via CYP3A4 for both paraoxon and *para*-nitrophenol.

The polar metabolites of parathion are excreted mainly in the urine in humans and experimental species. Several studies indicated that the remaining [^{14}C]-derived residues were negligible in experimental animal models within hours to days after administration of [^{14}C]-labelled parathion.

Parathion is not electrophilic, but its bioactive metabolite, paraoxon, can covalently modify B-esterases specifically at the active site serine residue; however, it is unknown whether the electrophilicity of paraoxon plays a role in carcinogenesis.

With respect to whether parathion is genotoxic, the evidence is *moderate*. In humans exposed to parathion and other pesticides in an occupational setting, chromosomal damage and sister-chromatid exchange were observed in one study. DNA and chromosomal damage were found in several studies in human cells (mostly lymphocytes) in vitro. Studies in experimental animals in vivo gave predominantly negative results for dominant lethal mutation and micronucleus formation in bone marrow. There were two in-vitro studies that gave positive results for chromosomal damage in rodent cells, although there were also studies that gave negative results. Studies of gene mutation in bacteria gave negative results for parathion, with or without metabolic activation.

The evidence is *weak* that parathion modulates receptor-mediated effects. Inhibition of acetylcholinesterase activity by paraoxon causes acute neurotoxicity in insects and mammalian species. Whether this is related to hyperplastic disease is unknown. No studies were identified in exposed humans. Studies using cultured human cells in vitro showed that parathion could antagonize the human androgen receptor. Parathion did not have nuclear receptor activity in one series of experiments. In Toxicity Forecaster (ToxCast™) assays, parathion showed appreciable activity in several assays for activity regarding nuclear and other receptors, including the aryl hydrocarbon receptor.

The evidence is *weak* that parathion induces oxidative stress, induces chronic inflammation, and is immunosuppressive. No studies in exposed humans were available to the Working Group. There were some studies showing positive effects in assays in vitro and in vivo; however, the database was too small to draw any firm conclusions. Several immune parameters in animal models in vivo, such as serum immunoglobulin levels, number of helper T cells and regulatory T cells, number of immunoglobulin E (IgE)-positive B cells, and cytokine levels were shown to be modulated after exposure to parathion.

The evidence is *strong* that parathion alters cell proliferation, cell death or nutrient supply. No studies in exposed humans were available to the Working Group. Sprague Dawley rats

(age, 39 days) treated with parathion exhibited a markedly increased density of terminal end buds compared with controls, at this time of active differentiation of terminal end bud into alveolar buds in the mammary gland. Studies using cultured human MCF-10F cells indicated that parathion could alter gene expression and cell proliferation. Treatment of human breast epithelial cell line MCF-10F with parathion resulted in increased levels of proliferating cell nuclear antigen and mutant TP53, an effect that was mitigated by atropine. In addition, several studies in cultured human and other mammalian cell lines indicated that treatment with parathion (or paraoxon) leads to the induction of apoptosis and cell death.

For the other key characteristics of human carcinogens, data were too few to allow evaluation.

There were no data on cancer-related susceptibility after exposure to parathion.

Overall, the mechanistic data provide some additional support for carcinogenicity findings of parathion.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of parathion.

6.2 Cancer in experimental animals

There is *sufficient evidence* for the carcinogenicity of parathion in experimental animals.

6.3 Overall evaluation

Parathion is *possibly carcinogenic to humans* (*Group 2B*).

References

Abbas R, Hayton WL (1997). A physiologically based pharmacokinetic and pharmacodynamic model for paraoxon in rainbow trout. *Toxicol Appl Pharmacol*, 145(1):192–201. doi:10.1006/taap.1997.8168 PMID:9221837

AgriBusiness Global Sourcing Network (2015). Parathion. Available from: http://www.agribusinessglobal.com/sourcing/research/parathion/.

Ahn J, Albanes D, Berndt SI, Peters U, Chatterjee N, Freedman ND, et al.; Prostate, Lung, Colorectal and Ovarian Trial Project Team (2009). Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. *Carcinogenesis*, 30(5):769–76. doi:10.1093/carcin/bgp055 PMID:19255064

Alavanja MC, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, et al. (2014). Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study. *PLoS ONE*, 9(10):e109332. doi:10.1371/journal.pone.0109332 PMID:25337994

Alavanja MC, Ross MK, Bonner MR (2013). Increased cancer burden among pesticide applicators and others due to pesticide exposure. *CA Cancer J Clin*, 63(2):120–42. doi:10.3322/caac.21170 PMID:23322675

Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. (1996). The Agricultural Health Study. *Environ Health Perspect*, 104(4):362–9. doi:10.1289/ehp.96104362 PMID:8732939

Arcury TA, Grzywacz JG, Barr DB, Tapia J, Chen H, Quandt SA (2007). Pesticide urinary metabolite levels of children in eastern North Carolina farmworker households. *Environ Health Perspect*, 115(8):1254–60. doi:10.1289/ehp.9975 PMID:17687456

Arcury TA, Grzywacz JG, Davis SW, Barr DB, Quandt SA (2006). Organophosphorus pesticide urinary metabolite levels of children in farmworker households in eastern North Carolina. *Am J Ind Med*, 49(9):751–60. doi:10.1002/ajim.20354 PMID:16804908

Areekul S, Srichairat S, Kirdudom P (1981). Serum and red cell cholinesterase activity in people exposed to organophosphate insecticides. *Southeast Asian J Trop Med Public Health*, 12(1):94–8. PMID:7256362

Arterberry JD, Durham WF, Elliott JW, Wolfe HR (1961). Exposure to parathion. Measurement by blood cholinesterase level and urinary p-nitrophenol excretion. *Arch Environ Health*, 3(4):476–85. doi:10.1080/00039896.1961.10663054 PMID:13862642

Atkinson JE, Bolte HF, Rubin LF, Sonawane M (1994). Assessment of ocular toxicity in dogs during 6 months' exposure to a potent organophosphate. *J Appl Toxicol*, 14(2):145–52. doi:10.1002/jat.2550140217 PMID:8027510

Attia AM (2000). Possible involvement of beta-adrenergic receptors in the enhancement of nocturnal pineal

N-acetyltransferase activity due to parathion administration. *Toxicology*, 142(2):79–86. doi:10.1016/S0300-483X(99)00106-7 PMID:10685507

Attia AM, Mostafa MH, Richardson BA, Reiter RJ (1995). Changes in nocturnal pineal indoleamine metabolism in rats treated with parathion are prevented by beta-adrenergic antagonist administration. *Toxicology*, 97(1-3):183–9. doi:10.1016/0300-483X(94)02947-S PMID:7716784

Attia AM, Reiter RJ, Stokkan KA, Mostafa MH, Soliman SA, el-Sebae AK (1991). Parathion (O,O-dimethyl-O-p-nitrophenyl phosphorothioate) induces pineal melatonin synthesis at night. *Brain Res Bull*, 26(4):553–7. doi:10.1016/0361-9230(91)90095-2 PMID:1714339

Bai Y, Zhou L, Wang J (2006). Organophosphorus pesticide residues in market foods in Shaanxi area, China. *Food Chem*, 98(2):240–2. doi:10.1016/j.foodchem.2005.05.070

Band PR, Abanto Z, Bert J, Lang B, Fang R, Gallagher RP, et al. (2011). Prostate cancer risk and exposure to pesticides in British Columbia farmers. *Prostate*, 71(2):168–83. doi:10.1002/pros.21232 PMID:20799287

Banks CN, Lein PJ (2012). A review of experimental evidence linking neurotoxic organophosphorus compounds and inflammation. *Neurotoxicology*, 33(3):575–84. doi:10.1016/j.neuro.2012.02.002 PMID:22342984

Barnes JM, Denz FA (1951). The chronic toxicity of p-nitrophenyl diethyl thiophosphate (E. 605); a long-term feeding experiment with rats. *J Hyg (Lond)*, 49(4):430–41. doi:10.1017/S0022172400066742 PMID:14908051

Bartsch H, Malaveille C, Camus AM, Martel-Planche G, Brun G, Hautefeuille A, et al. (1980). Validation and comparative studies on 180 chemicals with *S. typhimurium* strains and V79 Chinese hamster cells in the presence of various metabolizing systems. *Mutat Res*, 76(1):1–50. doi:10.1016/0165-1110(80)90002-0 PMID:6993936

Beane Freeman LE, Dennis LK, Lynch CF, Thorne PS, Just CL (2004). Toenail arsenic content and cutaneous melanoma in Iowa. *Am J Epidemiol*, 160(7):679–87. doi:10.1093/aje/kwh267 PMID:15383412

Bonini MG, Rota C, Tomasi A, Mason RP (2006). The oxidation of 2′,7′-dichlorofluorescin to reactive oxygen species: a self-fulfilling prophesy? *Free Radic Biol Med*, 40(6):968–75. doi:10.1016/j.freeradbiomed.2005.10.042 PMID:16540392

Bradman A, Barr DB, Claus Henn BG, Drumheller T, Curry C, Eskenazi B (2003). Measurement of pesticides and other toxicants in amniotic fluid as a potential biomarker of prenatal exposure: a validation study. *Environ Health Perspect*, 111(14):1779–82. doi:10.1289/ehp.6259 PMID:14594631

Bradway DE, Shafik TM, Lores EM (1977). Comparison of cholinesterase activity, residue levels, and urinary metabolite excretion of rats exposed to organophosphorus pesticides. *J Agric Food Chem*, 25(6):1353–8. doi:10.1021/jf60214a007 PMID:72085

Braeckman RA, Audenaert F, Willems JL, Belpaire FM, Bogaert MG (1983). Toxicokinetics of methyl parathion and parathion in the dog after intravenous and oral administration. *Arch Toxicol*, 54(1):71–82. doi:10.1007/BF00277817 PMID:6639354

Brand RM, Pike J, Wilson RM, Charron AR (2003). Sunscreens containing physical UV blockers can increase transdermal absorption of pesticides. *Toxicol Ind Health*, 19(1):9–16. doi:10.1191/0748233703th169oa PMID:15462532

Bravo R, Caltabiano LM, Weerasekera G, Whitehead RD, Fernandez C, Needham LL, et al. (2004). Measurement of dialkyl phosphate metabolites of organophosphorus pesticides in human urine using lyophilization with gas chromatography-tandem mass spectrometry and isotope dilution quantification. *J Expo Anal Environ Epidemiol*, 14(3):249–59. doi:10.1038/sj.jea.7500322 PMID:15141154

Bustos-Obregón E, Díaz O, Sobarzo C (2001). Parathion induces mouse germ cells apoptosis. *Ital J Anat Embryol*, 106(Suppl 2):199–204. PMID:11732577

Butler AM, Murray M (1997). Biotransformation of parathion in human liver: participation of CYP3A4 and its inactivation during microsomal parathion oxidation. *J Pharmacol Exp Ther*, 280(2):966–73. PMID:9023313

Cabello G, Valenzuela M, Vilaxa A, Durán V, Rudolph I, Hrepic N, et al. (2001). A rat mammary tumor model induced by the organophosphorous pesticides parathion and malathion, possibly through acetylcholinesterase inhibition. *Environ Health Perspect*, 109(5):471–9. doi:10.1289/ehp.01109471 PMID:11401758

Calaf GM, Roy D (2007a). Gene and protein expressions induced by 17beta-estradiol and parathion in cultured breast epithelial cells. *Mol Med*, 13(5–6):255–65. doi:10.2119/2006-00087.Calaf PMID:17622325

Calaf GM, Roy D (2007b). Gene expression signature of parathion-transformed human breast epithelial cells. *Int J Mol Med*, 19(5):741–50. PMID:17390078

Calaf GM, Roy D (2008a). Cancer genes induced by malathion and parathion in the presence of estrogen in breast cells. *Int J Mol Med*, 21(2):261–8. PMID:18204794

Calaf GM, Roy D (2008b). Cell adhesion proteins altered by 17beta estradiol and parathion in breast epithelial cells. *Oncol Rep*, 19(1):165–9. PMID:18097591

California Department of Pesticide Regulation (2015). Surface Water Database (SURF). Surface Water Protection Program. California Department of Pesticide Regulation. Available from: http://www.cdpr.ca.gov/docs/emon/surfwtr/surfdata.htm, accessed March 2015.

Canales-Aguirre AA, Gomez-Pinedo UA, Luquin S, Ramírez-Herrera MA, Mendoza-Magaña ML, Feria-Velasco A (2012). Curcumin protects against the oxidative damage induced by the pesticide parathion in the

hippocampus of the rat brain. *Nutr Neurosci*, 15(2):62–9. doi:10.1179/1476830511Y.0000000034 PMID:22333997

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, et al. (1992). Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res*, 52(9):2447–55. PMID:1568215

Carlson K, Jortner BS, Ehrich M (2000). Organophosphorus compound-induced apoptosis in SH-SY5Y human neuroblastoma cells. *Toxicol Appl Pharmacol*, 168(2):102–13. doi:10.1006/taap.2000.8997 PMID:11032765

Carver MP, Riviere JE (1989). Percutaneous absorption and excretion of xenobiotics after topical and intravenous administration to pigs. *Fundam Appl Toxicol*, 13(4):714–22. doi:10.1016/0272-0590(89)90329-1 PMID:2620792

Casale GP, Cohen SD, DiCapua RA (1983). The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erythrocytes in inbred mice. *Toxicol Appl Pharmacol*, 68(2):198–205. doi:10.1016/0041-008X(83)90004-2 PMID:6857660

Casale GP, Cohen SD, DiCapua RA (1984). Parathion-induced suppression of humoral immunity in inbred mice. *Toxicol Lett*, 23(2):239–47. doi:10.1016/0378-4274(84)90133-4 PMID:6506099

Casale GP, Vennerstrom JL, Bavari S, Wang TL (1993). Inhibition of interleukin 2 driven proliferation of mouse CTLL2 cells, by selected carbamate and organophosphate insecticides and congeners of carbaryl. *Immunopharmacol Immunotoxicol*, 15(2–3):199–215. doi:10.3109/08923979309025994 PMID:8349949

Casida JE, Quistad GB (2004). Organophosphate toxicology: safety aspects of nonacetylcholinesterase secondary targets. *Chem Res Toxicol*, 17(8):983–98. doi:10.1021/tx0499259 PMID:15310231

Cehovic G, Dettbarn WD, Welsch F (1972). Paraoxon: effects on rat brain cholinesterase and on growth hormone and prolactin of pituitary. *Science*, 15:1256–58. PMID:5061247

Chang SK, Williams PL, Dauterman WC, Riviere JE (1994). Percutaneous absorption, dermatopharmacokinetics and related bio-transformation studies of carbaryl, lindane, malathion, and parathion in isolated perfused porcine skin. *Toxicology*, 91(3):269–80. doi:10.1016/0300-483X(94)90014-0 PMID:7521545

Chen Y, Graziano JH, Parvez F, Hussain I, Momotaj H, van Geen A, et al. (2006). Modification of risk of arsenic-induced skin lesions by sunlight exposure, smoking, and occupational exposures in Bangladesh. *Epidemiology*, 17(4):459–67. doi:10.1097/01.ede.0000220554.50837.7f PMID:16755266

Cohen B, Richter E, Weisenberg E, Schoenberg J, Luria M (1979). Sources of parathion exposures for Israeli aerial spray workers, 1977. *Pestic Monit J*, 13(3):81–6. PMID:537865

Contreras HR, Paredes V, Urquieta B, Del Valle L, Bustos-Obregón E (2006). Testosterone production and spermatogenic damage induced by organophosphorate pesticides. *Biocell*, 30(3):423–9. PMID:17375462

Costa LG, Giordano G, Cole TB, Marsillach J, Furlong CE (2013). Paraoxonase 1 (PON1) as a genetic determinant of susceptibility to organophosphate toxicity. *Toxicology*, 307:115–22. doi:10.1016/j.tox.2012.07.011 PMID:22884923

Crow JA, Bittles V, Herring KL, Borazjani A, Potter PM, Ross MK (2012). Inhibition of recombinant human carboxylesterase 1 and 2 and monoacylglycerol lipase by chlorpyrifos oxon, paraoxon and methyl paraoxon. *Toxicol Appl Pharmacol*, 258(1):145–50. doi:10.1016/j.taap.2011.10.017 PMID:22100607

Crow JA, Borazjani A, Potter PM, Ross MK (2007). Hydrolysis of pyrethroids by human and rat tissues: examination of intestinal, liver and serum carboxylesterases. *Toxicol Appl Pharmacol*, 221(1):1–12. doi:10.1016/j.taap.2007.03.002 PMID:17442360

Darko G, Akoto O (2008). Dietary intake of organophosphorus pesticide residues through vegetables from Kumasi, Ghana. *Food Chem Toxicol*, 46(12):3703–6. doi:10.1016/j.fct.2008.09.049 PMID:18929615

Degraeve N, Moutschen J, Moutschen-Dahmen M, Gilot-Delhalle J, Colizzi A, Houbrechts N, et al. (1979). Genetic effects of organophosphate insecticides in mouse. *Mutat Res*, 64(2):131. doi:10.1016/0165-1161(79)90053-0

Dennis LK, Lynch CF, Sandler DP, Alavanja MC (2010). Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. *Environ Health Perspect*, 118(6):812–7. doi:10.1289/ehp.0901518 PMID:20164001

Deskin R, Rosenstein L, Rogers N, Westbrook B (1978). Parathion toxicity in perinatal rats born to spontaneously hypertensive dams. *J Environ Pathol Toxicol*, 2(2):291–300. PMID:739214

Durham WF, Wolfe HR, Elliott JW (1972). Absorption and excretion of parathion by spraymen. *Arch Environ Health*, 24(6):381–7. doi:10.1080/00039896.1972.10666113 PMID:5031564

Eaton DL (2000). Biotransformation enzyme polymorphism and pesticide susceptibility. *Neurotoxicology*, 21(1–2):101–11. PMID:10794390

Edwards FL, Yedjou CG, Tchounwou PB (2013). Involvement of oxidative stress in methyl parathion and parathion-induced toxicity and genotoxicity to human liver carcinoma ($HepG_2$) cells. *Environ Toxicol*, 28(6):342–8. doi:10.1002/tox.20725 PMID:21544925

EFSA (2011). The 2011 European Union Report on Pesticide Residues in Food. Parma: European Food Safety Authority. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/3694.htm, accessed 27 April 2015.

Eigenberg DA, Pazdernik TL, Doull J (1983). Hemoperfusion and pharmacokinetic studies with

parathion and paraoxon in the rat and dog. *Drug Metab Dispos*, 11(4):366–70. PMID:6137345

Elliott JW, Walker KC, Penick AE, Durham WF (1960). Insecticide exposure, a sensitive procedure for urinary *p*-nitrophenol determination as a measure of exposure to parathion. *J Agric Food Chem*, 8(2):111–3. doi:10.1021/jf60108a011

Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, et al. (2005). Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. *Am J Epidemiol*, 161(2):121–35. doi:10.1093/aje/kwi022 PMID:15632262

EPA (1984). Ethyl parathion, review of chronic/oncogenic rat study. Memorandum. Reg. No. 524-27, 132, 144 Accession #252702, 703, 704, 705. William Burnam. Toxicology Branch (ed). Document No. 003948. Washington (DC): United States Environmental Protection Agency. Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/057501/057501-001.pdf.

EPA (1986a). Parathion, rereading of thyroid slides for thyroid follicular adenomas in the chronic rat study. Memorandum – Robert Zendzian. Toxicology Branch. Document No. 005109. Washington (DC): United States Environmental Protection Agency.

EPA (1986b). Parathion light and electron microscopic examination of tissue from the eye of rats completing a two-year feeding study. MRID 4088701. Washington (DC): United States Environmental Protection Agency.

EPA (1986c). Parathion: study for chronic toxicity and cancerogenicity in Wistar rats (administration in diet for twenty-six months): Report No. 16305. MRID 40644704. Author, Eiben R. Peer reviewed by EPA. Available from: https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data.

EPA (1988). Parathion, mutagenicity studies. CHO/HGPRT mutation assay. Memorandum from Robert Zendzian. Document No. 057501. MRID 406447-06. Washington (DC): United States Environmental Protection Agency.

EPA (1989a). Parathion, chronic/oncogenicity study in rats. Memorandum from Robert Zendzian. Document No. 007096. Washington (DC): Office of Pesticides and Toxic Substances, United States Environmental Protection Agency.

EPA (1989b). Second peer review of parathion. Memorandum from Esther Rinde. Science Analysis and Coordination Branch. Document No. 007840. Washington (DC): United States Environmental Protection Agency. Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/057501/057501-019.pdf.

EPA (1990). Two generation reproduction study of ethyl parathion technical administered in the diet to CD (Sprague-Dawley) rats: Lab Project Nos. 52-630: 88-88-42001; 88-88-42002. Author, Neeper-Bradley T. MRID 41418501. Peer reviewed by EPA. Available from: https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data.

EPA (1991a). Carcinogenicity peer review of parathion (3rd). Memorandum from Esther Rinde. Science Analysis & Coordination Branch. Washington (DC): United States Environmental Protection Agency. Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/057501/057501-024.pdf.

EPA (1991b). A three month oral toxicity study in rats via the diet with ethyl parathion to investigate ocular effects and cholinesterase activity. Author, Atkinson JE. Lab. Project No. 89-3469. MRID 41834501. Peer reviewed by EPA. Available from: https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data.

EPA (2000a). RED facts: ethyl parathion. prevention, pesticides and toxic substances. EPA-738-F00-009. September 2000. Washington (DC): United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/0155fct.pdf, accessed 5 January 2016.

EPA (2000b). Parathion. Hazard summary. Available from: https://www.epa.gov/sites/production/files/2016-09/documents/parathion.pdf.

EPA (2007). Method 8141B: Organophosphorus compounds by gas chromatography (revision 2). Test methods for evaluating solid waste, physical/chemical methods. SW-846. Final update IV. Washington (DC): Office of Resource Conservation and Recovery, United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/production/files/2015-12/documents/8141b.pdf.

EPA (2016a). Chemical Dashboard. Washington (DC): Chemical Safety for Sustainability, United States Environmental Protection Agency. Online database. Available from: https://comptox.epa.gov/dashboard.

EPA (2016b). Toxicity Forecaster (ToxCastTM) Data. Washington (DC): United States Environmental Protection Agency. Online database. Available from: https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data.

Eyer F, Meischner V, Kiderlen D, Thiermann H, Worek F, Haberkorn M, et al. (2003). Human parathion poisoning. A toxicokinetic analysis. *Toxicol Rev*, 22(3):143–63. doi:10.2165/00139709-200322030-00003 PMID:15181664

FAO (1997). Decision guidance documents: methamidophos - methyl parathion - monocrotophos - parathion - phosphamidon. Joint FAO/UNEP Programme for the Operation of Prior Informed Consent (PIC). Rome: Food and Agriculture Organization of the United Nations. Available from: http://www.fao.org/docrep/w5715e/w5715e00.htm, accessed: 31 January 2015.

FAO/UNEP (2005). Decision guidance document: parathion. Secretariat for the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International

Trade. Joint FAO/UNEP Programme for the Operation of Prior Informed Consent. Available from: http://www.pic.int/Portals/5/DGDs/DGD_Parathion_EN.pdf, accessed 31 January 2015.

FDA (2015). Total Diet Study analytical results. Pesticide residues and industrial chemicals 1991–2003. Silver Spring (MD): United States Food and Drug Administration Available from: http://www.fda.gov/downloads/Food/FoodScienceResearch/TotalDietStudy/UCM184304.pdf, accessed 22 February 2016.

Fenske RA, Lu C, Barr D, Needham L (2002). Children's exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. *Environ Health Perspect*, 110(5):549–53. doi:10.1289/ehp.02110549 PMID:12003762

Fernandez-Cabezudo MJ, Azimullah S, Nurulain SM, Mechkarska M, Lorke DE, Hasan MY, et al. (2008). The organophosphate paraoxon has no demonstrable effect on the murine immune system following subchronic low dose exposure. *Int J Immunopathol Pharmacol*, 21(4):891–901. PMID:19144274

Fernandez-Cabezudo MJ, Lorke DE, Azimullah S, Mechkarska M, Hasan MY, Petroianu GA, et al. (2010). Cholinergic stimulation of the immune system protects against lethal infection by *Salmonella enterica serovar Typhimurium*. *Immunology*, 130(3):388–98. doi:10.1111/j.1365-2567.2009.03238.x PMID:20408892

Fillion J, Sauvé F, Selwyn J (2000). Multiresidue method for the determination of residues of 251 pesticides in fruits and vegetables by gas chromatography/mass spectrometry and liquid chromatography with fluorescence detection. *J AOAC Int*, 83(3):698–713. PMID:10868594

Flaskos J, McLean WG, Hargreaves AJ (1994). The toxicity of organophosphate compounds towards cultured PC12 cells. *Toxicol Lett*, 70(1):71–6. doi:10.1016/0378-4274(94)90146-5 PMID:8310459

Foxenberg RJ, Ellison CA, Knaak JB, Ma C, Olson JR (2011). Cytochrome P450-specific human PBPK/PD models for the organophosphorus pesticides: chlorpyrifos and parathion. *Toxicology*, 285(1–2):57–66. doi:10.1016/j.tox.2011.04.002 PMID:21514354

Fredriksson T, Bigelow JK (1961). Tissue distribution of P^{32}-labeled parathion. Autoradiographic technique. *Arch Environ Health*, 2(6):663–7. doi:10.1080/00039896.1961.10662923 PMID:13701584

Fukuyama T, Kosaka T, Miyashita L, Nishino R, Wada K, Hayashi K, et al. (2012). Role of regulatory T cells in the induction of atopic dermatitis by immunosuppressive chemicals. *Toxicol Lett*, 213(3):392–401. doi:10.1016/j.toxlet.2012.07.018 PMID:22842586

Fukuyama T, Tajima Y, Ueda H, Hayashi K, Kosaka T (2011). Prior exposure to immunosuppressive organophosphorus or organochlorine compounds aggravates the T_H1- and T_H2-type allergy caused by topical sensitization to 2,4-dinitrochlorobenzene and trimellitic anhydride. *J Immunotoxicol*, 8(2):170–82. doi:10.3109/1547691X.2011.566231 PMID:21534883

Fukuyama T, Tajima Y, Ueda H, Hayashi K, Shutoh Y, Harada T, et al. (2010). Apoptosis in immunocytes induced by several types of pesticides. *J Immunotoxicol*, 7(1):39–56. doi:10.3109/15476910903321704 PMID:19911945

Gagné J, Brodeur J (1972). Metabolic studies on the mechanisms of increased susceptibility of weaning rats to parathion. *Can J Physiol Pharmacol*, 50(9):902–15. doi:10.1139/y72-129 PMID:5084365

Gallicchio VS, Casale GP, Watts T (1987b). Inhibition of human bone marrow-derived stem cell colony formation (CFU-E, BFU-E, and CFU-GM) following in vitro exposure to organophosphates. *Exp Hematol*, 15(11):1099–102. PMID:3678410

Gallicchio VS, Watts TD,, Casale GP, Bartholomew PM (1987a). Altered colony-forming activities of bone marrow hematopoietic stem cells in mice following short-term in vivo exposure to parathion. *Int J Cell Cloning*, 5(3):231–41. doi:10.1002/stem.5530050307 PMID:3598245

Garcia-Repetto R, Martinez D, Repetto M (1995). Coefficient of distribution of some organophosphorous pesticides in rat tissue. *Vet Hum Toxicol*, 37(3):226–9. PMID:7571350

Gilliom RJ, Barbash JE, Crawford CG, Hamilton PA, Martin JD, Nakagaki N, et al. (2006). Pesticides in the Nation's Streams and Ground Water, 1992–2001. Circular 1291. National Water Quality assessment program. US Department of the Interior, US Geological Survey. Available from: http://pubs.usgs.gov/circ/2005/1291/pdf/circ1291.pdf.

Gilot-Delhalle J, Colizzi A, Moutschen J, Moutschen-Dahmen M (1983). Mutagenicity of some organophosphorus compounds at the *ade6* locus of *Schizosaccharomyces* pombe. *Mutat Res*, 117(1–2):139–48. doi:10.1016/0165-1218(83)90161-1 PMID:6835257

Gyrd-Hansen N, Brimer L, Rasmussen F (1993). Percutaneous absorption of organophosphorus insecticides in pigs–the influence of different vehicles. *J Vet Pharmacol Ther*, 16(2):174–80. doi:10.1111/j.1365-2885.1993.tb00161.x PMID:8345567

Halpert J, Hammond D, Neal RA (1980). Inactivation of purified rat liver cytochrome P-450 during the metabolism of parathion (diethyl *p*-nitrophenyl phosphorothionate). *J Biol Chem*, 255(3):1080–9. PMID:6766135

Haney AF, Hughes SF, Hughes CL Jr (1984). Screening of potential reproductive toxicants by use of porcine granulosa cell cultures. *Toxicology*, 30(3):227–41. doi:10.1016/0300-483X(84)90094-5 PMID:6538705

Harbison RD (1975). Comparative toxicity of some selected pesticides in neonatal and adult rats. *Toxicol Appl Pharmacol*, 32(2):443–6. doi:10.1016/0041-008X(75)90234-3 PMID:1154405

Hayes WJ Jr, Laws ER Jr, editors (1991). Classes of Pesticides. Handbook of Pesticide Toxicology. Volume 2. New York (NY): Academic Press, Inc.; p. 1046. Available from: http://toxnet.nlm.nih.gov

Hazleton LW, Holland EG (1950). Pharmacology and toxicology of parathion. *Agricultural Control Chemicals*. Washington (DC): American Chemical Society; pp. 31–8. doi:10.1021/ba-1950-0001.ch009

Heltshe SL, Lubin JH, Koutros S, Coble JB, Ji B-T, Alavanja MC, et al. (2012). Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. *J Expo Sci Environ Epidemiol*, 22(4):409–16. doi:10.1038/jes.2012.31 PMID:22569205

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, et al. (1986). Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA*, 256(9):1141–7. doi:10.1001/jama.1986.03380090081023 PMID:3801091

Hoffmann U, Papendorf T (2006). Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med*, 32(3):464–8. doi:10.1007/s00134-005-0051-z PMID:16479380

HSDB (2016). Parathion. Toxnet Hazardous Substances Data Bank. Bethesda (MD): United States National Library of Medicine. Available from: https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm, accessed 21 November 2016.

Humbert R, Adler DA, Disteche CM, Hassett C, Omiecinski CJ, Furlong CE (1993). The molecular basis of the human serum paraoxonase activity polymorphism. *Nat Genet*, 3(1):73–6. doi:10.1038/ng0193-73 PMID:8098250

Hurh E, Lee EJ, Kim YG, Kim SY, Kim SH, Kim YC, et al. (2000a). Effects of neostigmine on the pharmacokinetics of intravenous parathion in rats. *Res Commun Mol Pathol Pharmacol*, 108(3–4):261–73. PMID:11913717

Hurh E, Lee EJ, Kim YG, Kim SY, Kim SH, Kim YC, et al. (2000b). Effects of physostigmine on the pharmacokinetics of intravenous parathion in rats. *Biopharm Drug Dispos*, 21(8):331–8. doi:10.1002/bdd.243 PMID:11514953

IARC (1983). Miscellaneous pesticides. *IARC Monogr Eval Carcinog Risk Chem Hum*, 30:1–424. Available from: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono30.pdf. PMID:6578175

IARC (1987). Overall evaluations of carcinogenicity: an updating of *IARC Monographs* volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7:1–440. Available from: http://monographs.iarc.fr/ENG/Monographs/suppl7/index.php. PMID:3482203

IARC (1991). Occupational exposures in insecticide application, and some pesticides. *IARC Monogr Eval Carcinog Risks Hum*, 53:1–612. Available from: http://monographs.iarc.fr/ENG/Monographs/vol53/.

IARC (2014). Table 1. Key characteristics of carcinogens. In: Section 4. Mechanistic and other data. Instructions for authors. Lyon: International Agency for Research on Cancer. Available from: http://monographs.iarc.fr/ENG/Preamble/previous/Instructions_to_Authors_S4.pdf.

IFA (2015). Parathion. GESTIS international limit values. Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung. Available from: http://limitvalue.ifa.dguv.de/.

IPCS (1992). Parathion health and safety guide (No. 74). United Nations Environment Programme. Geneva: International Labour Organization, International Programme on Chemical Safety, World Health Organization.

IPCS (2004). Parathion. International Chemical Safety Card (ICSC 0006). Geneva: International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/icsc/icsc/eics0006.htm.

Islas-González K, González-Horta C, Sánchez-Ramírez B, Reyes-Aragón E, Levario-Carrillo M (2005). In vitro assessment of the genotoxicity of ethyl paraoxon in newborns and adults. *Hum Exp Toxicol*, 24(6):319–24. doi:10.1191/0960327105ht534oa PMID:16004199

Jafari M, Salehi M, Asgari A, Ahmadi S, Abasnezhad M, Hajihoosani R, et al. (2012). Effects of paraoxon on serum biochemical parameters and oxidative stress induction in various tissues of Wistar and Norway rats. *Environ Toxicol Pharmacol*, 34(3):876–87. doi:10.1016/j.etap.2012.08.011 PMID:23021855

Jepson GW, Hoover DK, Black RK, McCafferty JD, Mahle DA, Gearhart JM (1994). A partition coefficient determination method for nonvolatile chemicals in biological tissues. *Fundam Appl Toxicol*, 22(4):519–24. doi:10.1006/faat.1994.1059 PMID:7520010

Kalyanaraman B, Darley-Usmar V, Davies KJ, Dennery PA, Forman HJ, Grisham MB, et al. (2012). Measuring reactive oxygen and nitrogen species with fluorescent probes: challenges and limitations. *Free Radic Biol Med*, 52(1):1–6. doi:10.1016/j.freeradbiomed.2011.09.030 PMID:22027063

Karami S, Andreotti G, Koutros S, Barry KH, Moore LE, Han S, et al. (2013). Pesticide exposure and inherited variants in vitamin D pathway genes in relation to prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 22(9):1557–66. doi:10.1158/1055-9965.EPI-12-1454 PMID:23833127

Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N, et al. (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*, 25(7):1287–302. doi:10.1021/tx3000939 PMID:22519603

Kawashima K, Fujii T (2004). Expression of non-neuronal acetylcholine in lymphocytes and its contribution to

the regulation of immune function. *Front Biosci*, 9(1–3):2063–85. doi:10.2741/1390 PMID:15353271

Kevekordes S, Gebel T, Pav K, Edenharder R, Dunkelberg H (1996). Genotoxicity of selected pesticides in the mouse bone-marrow micronucleus test and in the sister-chromatid exchange test with human lymphocytes in vitro. *Toxicol Lett*, 89(1):35–42. doi:10.1016/S0378-4274(96)03779-4 PMID:8952709

Kojima H, Katsura E, Takeuchi S, Niiyama K, Kobayashi K (2004). Screening for estrogen and androgen receptor activities in 200 pesticides by *in vitro* reporter gene assays using Chinese hamster ovary cells. *Environ Health Perspect*, 112(5):524–31. doi:10.1289/ehp.6649 PMID:15064155

Kojima H, Takeuchi S, Nagai T (2010). Endocrine-disrupting potential of pesticides via nuclear receptors and aryl hydrocarbon receptor *J Health Sci*, 56(4):374–86. doi:10.1248/jhs.56.374

Koutros S, Beane Freeman LE, Lubin JH, Heltshe SL, Andreotti G, Barry KH, et al. (2013). Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. *Am J Epidemiol*, 177(1):59–74. doi:10.1093/aje/kws225 PMID:23171882

Lassiter TL, Ryde IT, Mackillop EA, Brown KK, Levin ED, Seidler FJ, et al. (2008). Exposure of neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters the response to a high-fat diet in adulthood. *Environ Health Perspect*, 116(11):1456–62. doi:10.1289/ehp.11673 PMID:19057696

Lee BW, London L, Paulauskis J, Myers J, Christiani DC (2003). Association between human paraoxonase gene polymorphism and chronic symptoms in pesticide-exposed workers. *J Occup Environ Med*, 45(2):118–22. doi:10.1097/01.jom.0000052953.59271.e1 PMID:12625227

Lee WJ, Sandler DP, Blair A, Samanic C, Cross AJ, Alavanja MC (2007). Pesticide use and colorectal cancer risk in the Agricultural Health Study. *Int J Cancer*, 121(2):339–46. doi:10.1002/ijc.22635 PMID:17390374

Lessire F, Gustin P, Delaunois A, Bloden S, Nemmar A, Vargas M, et al. (1996). Relationship between parathion and paraoxon toxicokinetics, lung metabolic activity, and cholinesterase inhibition in guinea pig and rabbit lungs. *Toxicol Appl Pharmacol*, 138(2):201–10. doi:10.1006/taap.1996.0118 PMID:8658521

Li B, Sedlacek M, Manoharan I, Boopathy R, Duysen EG, Masson P, et al. (2005). Butyrylcholinesterase, paraoxonase, and albumin esterase, but not carboxylesterase, are present in human plasma. *Biochem Pharmacol*, 70(11):1673–84. doi:10.1016/j.bcp.2005.09.002 PMID:16213467

Li C, Taneda S, Suzuki AK, Furuta C, Watanabe G, Taya K (2006). Estrogenic and anti-androgenic activities of 4-nitrophenol in diesel exhaust particles. *Toxicol Appl Pharmacol*, 217(1):1–6. doi:10.1016/j.taap.2006.06.010 PMID:16884752

Li H, Zhang S (2001). In vitro cytotoxicity of the organophosphorus pesticide parathion to FG-9307 cells. *Toxicol In Vitro*, 15(6):643–7. doi:10.1016/S0887-2333(01)00090-X PMID:11698164

Li L, Cao Z, Jia P, Wang Z (2010). Calcium signals and caspase-12 participated in paraoxon-induced apoptosis in EL4 cells. *Toxicol In Vitro*, 24(3):728–36. doi:10.1016/j.tiv.2010.01.005 PMID:20079824

Li W, Tai L, Liu J, Gai Z, Ding G (2014). Monitoring of pesticide residues levels in fresh vegetable form Heibei Province, North China. *Environ Monit Assess*, 186(10):6341–9. doi:10.1007/s10661-014-3858-7 PMID:24869955

Li X, Li C, Suzuki AK, Taneda S, Watanabe G, Taya K (2009). 4-Nitrophenol isolated from diesel exhaust particles disrupts regulation of reproductive hormones in immature male rats. *Endocrine*, 36(1):98–102. doi:10.1007/s12020-009-9192-0 PMID:19404784

López-Granero C, Cañadas F, Cardona D, Yu Y, Giménez E, Lozano R, et al. (2013). Chlorpyrifos-, diisopropylphosphorofluoridate-, and parathion-induced behavioral and oxidative stress effects: are they mediated by analogous mechanisms of action? *Toxicol Sci*, 131(1):206–16. doi:10.1093/toxsci/kfs280 PMID:22986948

Metcalf RL (1981). Insect control technology. ln: Kirk RE, Othmer DF, editors. Encyclopedia of Chemical Technology, 3rd edition, Volume 13. New York: John Wiley & Sons, pp. 438–439, 485.

Morgan DP, Hetzler HL, Slach EF, Lin LI (1977). Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. *Arch Environ Contam Toxicol*, 6(2–3):159–73. doi:10.1007/BF02097758 PMID:900999

Munch JW, Grimmett PE, Munch DJ, Wendelken SC, Domino MM, Zaffiro AD, Zimmerman ML (2012). Method 525.3. Determination of semivolatile organic chemicals in drinking water by solid phase extraction and capillary column gas chromatography/mass spectrometry (GC/MS). Version 1.0. EPA Document No. EPA/600/R-12/010.

Munn S, Keefe TJ, Savage EP (1985). A comparative study of pesticide exposures in adults and youth migrant field workers. *Arch Environ Health*, 40(4):215–20. doi:10.1080/00039896.1985.10545921 PMID:4051576

Mutch E, Williams FM (2006). Diazinon, chlorpyrifos and parathion are metabolised by multiple cytochromes P450 in human liver. *Toxicology*, 224(1–2):22–32. doi:10.1016/j.tox.2006.04.024 PMID:16757081

Nabb DP, Stein WJ, Hayes WJ Jr (1966). Rate of skin absorption of parathion and paraoxon. *Arch Environ Health*, 12(4):501–5. doi:10.1080/00039896.1966.10664416 PMID:5906458

NCBI (2015). PubChem Open Chemistry Database. Compound summary for CID 991. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/991, accessed 5 March 2015.

Neal RA, Halpert J (1982). Toxicology of thiono-sulfur compounds. *Annu Rev Pharmacol Toxicol*, 22(1):321–39. doi:10.1146/annurev.pa.22.040182.001541 PMID:7044288

Ni Z, Li S, Liu Y, Tang Y, Pang D (1993). [Induction of micronucleus by organophosphorus pesticides both in vivo and in vitro.] *J West China University of Medical Sciences (JWCUMS) Hua Xi Yi Ke Da Xue Xue Bao*, 24(1):82–6. PMID:8340099

Nielsen P, Friis C, Gyrd-Hansen N, Kraul I (1991). Disposition of parathion in neonatal and young pigs. *Pharmacol Toxicol*, 69(4):233–7. PMID:1956875

NIOSH (1976). Criteria for a recommended standard. Occupational exposure to parathion. Washington (DC): United States Department of Health, Education and Welfare (DHEW), National Institute for Occupational Safety and Health. Pub. NIOSH; pp. 76–190.

NIOSH (1994). Method 5600: organophosphorus pesticides. In: NIOSH Manual of Analytical Methods (NMAM), Fourth Edition. Atlanta (GA): National Institute for Occupational Safety and Health. Available from: http://www.epa.gov/homeland-security-research/niosh-method-5600-organophosphorus-pesticides, accessed 19 February 2016.

Nishino R, Fukuyama T, Tajima Y, Miyashita L, Watanabe Y, Ueda H, et al. (2013). Prior oral exposure to environmental immunosuppressive chemicals methoxychlor, parathion, or piperonyl butoxide aggravates allergic airway inflammation in NC/Nga mice. *Toxicology*, 309:1–8. doi:10.1016/j.tox.2013.03.018 PMID:23583882

Nishio A, Uyeki EM (1981). Induction of sister chromatid exchanges in Chinese hamster ovary cells by organophosphate insecticides and their oxygen analogs. *J Toxicol Environ Health*, 8(5–6):939–46. doi:10.1080/15287398109530128 PMID:7338954

NIST (2011). Parathion. NIST Standard Reference Data. National Institute of Standards and Technology. Available from: http://webbook.nist.gov/cgi/cbook.cgi?ID=56-38-2, accessed March 2015.

NTP (1979). Bioassay of parathion for possible carcinogenicity. *Natl Cancer Inst Carcinog Tech Rep Ser*, 70:1–123. PMID:12830227

O'Neil MJ, Heckelman PE, Dobbelaar PH, et al. (2013). Parathion. In: Merck & Co WS, editor. 15th edition. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.

OECD (2004). The 2004 OECD list of high production volume chemicals. Paris: OECD Environment Directorate, Office of Economic Co-Operation and Development.

Oh YJ, Jung YJ, Kang JW, Yoo YS (2007). Investigation of the estrogenic activities of pesticides from Pal-dang reservoir by in vitro assay. *Sci Total Environ*, 388(1-3):8–15. doi:10.1016/j.scitotenv.2007.07.013 PMID:17904202

Olsson AO, Nguyen JV, Sadowski MA, Barr DB (2003). A liquid chromatography/electrospray ionization-tandem mass spectrometry method for quantification of specific organophosphorus pesticide biomarkers in human urine. *Anal Bioanal Chem*, 376(6):808–15. doi:10.1007/s00216-003-1978-y PMID:12811448

Pasquini R, Scassellati-Sforzolini G, Dolara P, Pampanella L, Villarini M, Caderni G, et al. (1994). Assay of linuron and a pesticide mixture commonly found in the Italian diet, for promoting activity in rat liver carcinogenesis. *Pharmacol Toxicol*, 75(3–4):170–6. doi:10.1111/j.1600-0773.1994.tb00342.x PMID:7800659

Peña-Egido MJ, Mariño-Hernandez EL, Santos-Buelga C, Rivas-Gonzalo JC (1988b). Urinary excretion kinetics of *p*-nitrophenol following oral administration of parathion in the rabbit. *Arch Toxicol*, 62(5):351–4. doi:10.1007/BF00293622 PMID:3242444

Peña-Egido MJ, Rivas-Gonzalo JC, Mariño-Hernandez EL (1988a). Toxicokinetics of parathion in the rabbit. *Arch Toxicol*, 61(3):196–200. doi:10.1007/BF00316634 PMID:3355364

Pérez-Herrera N, Polanco-Minaya H, Salazar-Arredondo E, Solís-Heredia MJ, Hernández-Ochoa I, Rojas-García E, et al. (2008). PON1Q192R genetic polymorphism modifies organophosphorous pesticide effects on semen quality and DNA integrity in agricultural workers from southern Mexico. *Toxicol Appl Pharmacol*, 230(2):261–8. doi:10.1016/j.taap.2008.02.021 PMID:18430447

Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A (1994). Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). *Cancer Causes Control*, 5(4):310–8. doi:10.1007/BF01804981 PMID:8080942

Poet TS, Kousba AA, Dennison SL, Timchalk C (2004). Physiologically based pharmacokinetic/pharmacodynamic model for the organophosphorus pesticide diazinon. *Neurotoxicology*, 25(6):1013–30. doi:10.1016/j.neuro.2004.03.002 PMID:15474619

Pomeroy-Black M, Ehrich M (2012). Organophosphorus compound effects on neurotrophin receptors and intracellular signalling. *Toxicol In Vitro*, 26(5):759–65. doi:10.1016/j.tiv.2012.03.008 PMID:22449548

Poore RE, Neal RA (1972). Evidence for extrahepatic metabolism of parathion. *Toxicol Appl Pharmacol*, 23(4):759–68. doi:10.1016/0041-008X(72)90117-2 PMID:4644705

Pope CN (1999). Organophosphorus pesticides: do they all have the same mechanism of toxicity? *J Toxicol Environ Health B Crit Rev*, 2(2):161–81. doi:10.1080/109374099281205 PMID:10230392

Prins JM, Chao CK, Jacobson SM, Thompson CM, George KM (2014). Oxidative stress resulting from exposure of a human salivary gland cells to paraoxon: an *in vitro* model for organophosphate oral exposure. *Toxicol In Vitro*, 28(5):715–21. doi:10.1016/j.tiv.2014.01.009 PMID:24486155

Proskocil BJ, Bruun DA, Jacoby DB, van Rooijen N, Lein PJ, Fryer AD (2013). Macrophage TNF-α mediates

parathion-induced airway hyperreactivity in guinea pigs. *Am J Physiol Lung Cell Mol Physiol*, 304(8):L519–29. doi:10.1152/ajplung.00381.2012 PMID:23377347

Proskocil BJ, Bruun DA, Lorton JK, Blensly KC, Jacoby DB, Lein PJ, et al. (2008). Antigen sensitization influences organophosphorus pesticide-induced airway hyperreactivity. *Environ Health Perspect*, 116(3):381–8. doi:10.1289/ehp.10694 PMID:18335107

Qian Y, Venkatraj J, Barhoumi R, Pal R, Datta A, Wild JR, et al. (2007). Comparative non-cholinergic neurotoxic effects of paraoxon and diisopropyl fluorophosphate (DFP) on human neuroblastoma and astrocytoma cell lines. *Toxicol Appl Pharmacol*, 219(2–3):162–71. doi:10.1016/j.taap.2006.11.030 PMID:17223147

Qiao GL, Williams PL, Riviere JE (1994). Percutaneous absorption, biotransformation, and systemic disposition of parathion *in vivo* in swine. I. Comprehensive pharmacokinetic model. *Drug Metab Dispos*, 22(3):459–71. PMID:8070325

Quinby GE, Lemmon AB (1958). Parathion residues as a cause of poisoning in crop workers. *J Am Med Assoc*, 166(7):740–6. doi:10.1001/jama.1958.02990070026007 PMID:13502056

Quistad GB, Nomura DK, Sparks SE, Segall Y, Casida JE (2002). Cannabinoid CB1 receptor as a target for chlorpyrifos oxon and other organophosphorus pesticides. *Toxicol Lett*, 135(1-2):89–93. doi:10.1016/S0378-4274(02)00251-5 PMID:12243867

Rawn DFK, Cao XL, Doucet J, Davies DJ, Sun WF, Dabeka RW, et al. (2004). Canadian Total Diet Study in 1998: pesticide levels in foods from Whitehorse, Yukon, Canada, and corresponding dietary intake estimates. *Food Addit Contam*, 21(3):232–50. doi:10.1080/02652030310001655470 PMID:15195471

Reif DM, Martin MT, Tan SW, Houck KA, Judson RS, Richard AM, et al. (2010). Endocrine profiling and prioritization of environmental chemicals using ToxCast data. *Environ Health Perspect*, 118(12):1714–20. doi:10.1289/ehp.1002180 PMID:20826373

Reif DM, Sypa M, Lock EF, Wright FA, Wilson A, Cathey T, et al. (2013). ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence. *Bioinformatics*, 29(3):402–3. doi:10.1093/bioinformatics/bts686 PMID:23202747

Richter ED, Cohen B, Luria M, Schoenberg J, Weisenberg E, Gordon M (1980). Exposures of aerial spray workers to parathion. *Isr J Med Sci*, 16(2):96–100. PMID:7364572

Rodriguez H, Bustos-Obregon E (2000). An *in vitro* model to evaluate the effect of an organophosphoric agropesticide on cell proliferation in mouse seminiferous tubules. *Andrologia*, 32(1):1–5. doi:10.1111/j.1439-0272.2000.tb02857.x PMID:10702859

Rodriguez H, Guzman M, Espinoza O (2006). Parathion effects on protein synthesis in the seminiferous tubules of mice. *Ecotoxicol Environ Saf*, 65(1):129–33. doi:10.1016/j.ecoenv.2005.05.024 PMID:16029889

Rojas-García AE, Sordo M, Vega L, Quintanilla-Vega B, Solis-Heredia M, Ostrosky-Wegman P (2009). The role of paraoxonase polymorphisms in the induction of micronucleus in paraoxon-treated human lymphocytes. *Environ Mol Mutagen*, 50(9):823–9. doi:10.1002/em.20492 PMID:19402156

Ross MK, Borazjani A, Wang R, Crow JA, Xie S (2012). Examination of the carboxylesterase phenotype in human liver. *Arch Biochem Biophys*, 522(1):44–56. doi:10.1016/j.abb.2012.04.010 PMID:22525521

Rumack BH (2015). POISINDEX(R) Information System Micromedex, Inc., Englewood, CO, 2015; CCIS Volume 164, edition expires May, 2015. Hall AH & Rumack BH Eds. TOMES(R) Information System Micromedex, Inc., Englewood, CO, 2015. Available from: http://toxnet.nlm.nih.gov/.

Rupa DS, Rita P, Reddy PP, Reddi OS (1988). Screening of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes of vegetable garden workers. *Hum Toxicol*, 7(4):333–6. doi:10.1177/096032718800700406 PMID:3410481

Sadri S, Bahrami F, Khazaei M, Hashemi M, Asgari A (2010). Cannabinoid receptor agonist WIN-55,212–2 protects differentiated PC12 cells from organophosphorus- induced apoptosis. *Int J Toxicol*, 29(2):201–8. doi:10.1177/1091581809359708 PMID:20335515

Saleh AM, Vijayasarathy C, Fernandez-Cabezudo M, Taleb M, Petroianu G (2003a). Influence of paraoxon (POX) and parathion (PAT) on apoptosis: a possible mechanism for toxicity in low-dose exposure. *J Appl Toxicol*, 23(1):23–9. doi:10.1002/jat.880 PMID:12518333

Saleh AM, Vijayasarathy C, Masoud L, Kumar L, Shahin A, Kambal A (2003b). Paraoxon induces apoptosis in EL4 cells via activation of mitochondrial pathways. *Toxicol Appl Pharmacol*, 190(1):47–57. doi:10.1016/S0041-008X(03)00126-1 PMID:12831782

Schein LG, Donovan MP, Thomas JA, Felice PR (1980). Effects of pesticides on ^{3}H-dihydrotestosterone binding to cytosol proteins from various tissues of the mouse. *J Environ Pathol Toxicol*, 3(1-2):461–70. PMID:232714

Selgrade MK, Daniels MJ, Illing JW, Ralston AL, Grady MA, Charlet E, et al. (1984). Increased susceptibility to parathion poisoning following murine cytomegalovirus infection. *Toxicol Appl Pharmacol*, 76(2):356–64. doi:10.1016/0041-008X(84)90017-6 PMID:6093289

Simcox NJ, Fenske RA, Wolz SA, Lee IC, Kalman DA (1995). Pesticides in household dust and soil: exposure pathways for children of agricultural families. *Environ Health Perspect*, 103(12):1126–34. doi:10.1289/ehp.951031126 PMID:8747019

Singh S, Kumar V, Singh P, Banerjee BD, Rautela RS, Grover SS, et al. (2012). Influence of *CYP2C9*, *GSTM1*, *GSTT1* and *NAT2* genetic polymorphisms on DNA damage in workers occupationally exposed to organophosphate pesticides. *Mutat Res*, 741(1-2):101–8. doi:10.1016/j.mrgentox.2011.11.001 PMID:22108250

Singh S, Kumar V, Thakur S, Banerjee BD, Rautela RS, Grover SS, et al. (2011a). Paraoxonase-1 genetic polymorphisms and susceptibility to DNA damage in workers occupationally exposed to organophosphate pesticides. *Toxicol Appl Pharmacol*, 252(2):130–7. doi:10.1016/j.taap.2011.01.014 PMID:21291901

Singh S, Kumar V, Vashisht K, Singh P, Banerjee BD, Rautela RS, et al. (2011b). Role of genetic polymorphisms of *CYP1A1*, *CYP3A5*, *CYP2C9*, *CYP2D6*, and *PON1* in the modulation of DNA damage in workers occupationally exposed to organophosphate pesticides. *Toxicol Appl Pharmacol*, 257(1):84–92. doi:10.1016/j.taap.2011.08.021 PMID:21907728

Sipes NS, Martin MT, Kothiya P, Reif DM, Judson RS, Richard AM, et al. (2013). Profiling 976 ToxCast chemicals across 331 enzymatic and receptor signaling assays. *Chem Res Toxicol*, 26(6):878–95. doi:10.1021/tx400021f PMID:23611293

Slotkin TA (2011). Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? *Reprod Toxicol*, 31(3):297–301. doi:10.1016/j.reprotox.2010.07.012 PMID:20850519

Slotkin TA, MacKillop EA, Ryde IT, Tate CA, Seidler FJ (2007). Screening for developmental neurotoxicity using PC12 cells: comparisons of organophosphates with a carbamate, an organochlorine, and divalent nickel. *Environ Health Perspect*, 115(1):93–101. doi:10.1289/ehp.9527 PMID:17366826

Sobti RC, Krishan A, Pfaffenberger CD (1982). Cytokinetic and cytogenetic effects of some agricultural chemicals on human lymphoid cells in vitro: organophosphates. *Mutat Res*, 102(1):89–102. doi:10.1016/0165-1218(82)90149-5 PMID:6981766

Stamper CR, Balduini W, Murphy SD, Costa LG (1988). Behavioral and biochemical effects of postnatal parathion exposure in the rat. *Neurotoxicol Teratol*, 10(3):261–6. doi:10.1016/0892-0362(88)90026-8 PMID:3211105

Stevens JT (1973). The effect of parathion on the metabolism of ^{3}H-testosterone by hepatic microsomal enzymes from the male mouse. *Pharmacology*, 10(4):220–5. doi:10.1159/000136442 PMID:4762217

Straif K, Loomis D, Guyton K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2014). Future priorities for the IARC Monographs. *Lancet Oncol*, 15(7):683–4. doi:10.1016/S1470-2045(14)70168-8

Sultatos LG, Kim B, Woods L (1990). Evaluation of estimations *in vitro* of tissue/blood distribution coefficients for organothiophosphate insecticides. *Toxicol Appl Pharmacol*, 103(1):52–5. doi:10.1016/0041-008X(90)90261-R PMID:2315932

Takeuchi S, Iida M, Yabushita H, Matsuda T, Kojima H (2008). *In vitro* screening for aryl hydrocarbon receptor agonistic activity in 200 pesticides using a highly sensitive reporter cell line, DR-EcoScreen cells, and in vivo mouse liver cytochrome P450–1A induction by propanil, diuron and linuron. *Chemosphere*, 74(1):155–65. doi:10.1016/j.chemosphere.2008.08.015 PMID:18835618

Takeuchi S, Matsuda T, Kobayashi S, Takahashi T, Kojima H (2006). *In vitro* screening of 200 pesticides for agonistic activity via mouse peroxisome proliferator-activated receptor (PPAR)alpha and PPARgamma and quantitative analysis of *in vivo* induction pathway. *Toxicol Appl Pharmacol*, 217(3):235–44. doi:10.1016/j.taap.2006.08.011 PMID:17084873

Thomas JA, Schein LG (1974). Effect of parathion on the uptake and metabolism of androgens in rodent sex accessory organs. *Toxicol Appl Pharmacol*, 29(1):53–8. doi:10.1016/0041-008X(74)90161-6 PMID:4283680

Thomas JA, Schein LG, Donovan MP (1977). Some actions on parathion and/or dieldrin on androgen metabolism. *Environ Res*, 13(3):441–50. doi:10.1016/0013-9351(77)90024-X PMID:880938

Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect*, 121(7):756–65. doi:10.1289/ehp.1205784 PMID:23603828

Timchalk C, Busby A, Campbell JA, Needham LL, Barr DB (2007). Comparative pharmacokinetics of the organophosphorus insecticide chlorpyrifos and its major metabolites diethylphosphate, diethylthiophosphate and 3,5,6-trichloro-2-pyridinol in the rat. *Toxicology*, 237(1–3):145–57. doi:10.1016/j.tox.2007.05.007 PMID:17590257

Timofeeva OA, Sanders D, Seemann K, Yang L, Hermanson D, Regenbogen S, et al. (2008). Persistent behavioral alterations in rats neonatally exposed to low doses of the organophosphate pesticide, parathion. *Brain Res Bull*, 77(6):404–11. doi:10.1016/j.brainresbull.2008.08.019 PMID:18817854

van der Merwe D, Riviere JE (2005). Effect of vehicles and sodium lauryl sulphate on xenobiotic permeability and stratum corneum partitioning in porcine skin. *Toxicology*, 206(3):325–35. doi:10.1016/j.tox.2004.07.011 PMID:15588923

Verbout NG, Jacoby DB (2012). Muscarinic receptor agonists and antagonists: effects on inflammation and immunity. *Handbook Exp Pharmacol*, 208(208):403–27. doi:10.1007/978-3-642-23274-9_17 PMID:22222708

Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, et al. (2001). Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes Control*, 12(6):509–17. doi:10.1023/A:1011293208949 PMID:11519759

Wagner ED, Repetny K, Tan JS, Gichner T, Plewa MJ (1997). Mutagenic synergy between paraoxon and mammalian or plant-activated aromatic amines. *Environ Mol Mutagen*, 30(3):312–20. doi:10.1002/(SICI)1098-2280(1997)30:3<312::AID-EM10>3.0.CO;2-G PMID:9366910

Ware GW, Morgan DP, Estesen BJ, Cahill WP (1974). Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. II. Azodrin, ethyl and methylparathion. *Arch Environ Contam Toxicol*, 2(2):117–29. doi:10.1007/BF01975466 PMID:4851905

Ware GW, Whitacre DM (2004). The Pesticide Book. 6th ed. Willoughby (Ohio): Meister Media Worldwide.

Warner JS (1975). Identification of impurities in technical-grade pesticides. ln: Substitute Chemical Program - the First Year of Progress. Proceedings of a Symposium, Vol. IV, Chemical Method Workshop (PB - 261 007), Washington (DC): United States Environmental Protection Agency.

Waters MD, Simmon VF, Mitchell AD, Jorgenson TA, Valencia R (1980). An overview of short-term tests for the mutagenic and carcinogenic potential of pesticides. *J Environ Sci Health B*, 15(6):867–906. doi:10.1080/03601238009372221 PMID:7002991

Weast RC, editor (1988). Handbook of Chemistry and Physics. 69th edition. Boca Raton (FL): CRC Press Inc., 1988–1989, p. C-390.

Welch RM, Levin W, Conney AH (1967). Insecticide inhibition and stimulation of steroid hydroxylases in rat liver. *J Pharmacol Exp Ther*, 155(1):167–73. PMID:6017337

Wester RM, Tanojo H, Maibach HI, Wester RC (2000). Predicted chemical warfare agent VX toxicity to uniformed soldier using parathion in vitro human skin exposure and absorption. *Toxicol Appl Pharmacol*, 168(2):149–52. doi:10.1006/taap.2000.9028 PMID:11032770

Wiltrout RW, Ercegovich CD, Ceglowski WS (1978). Humoral immunity in mice following oral administration of selected pesticides. *Bull Environ Contam Toxicol*, 20(3):423–31. doi:10.1007/BF01683542 PMID:708932

Wolfe HR, Durham WF, Armstrong JF (1967). Exposure of workers to pesticides. *Arch Environ Health*, 14(4):622–33. doi:10.1080/00039896.1967.10664801 PMID:6024487

Wolfe HR, Durham WF, Armstrong JF (1970). Urinary excretion of insecticide metabolites. Excretion of para-nitrophenol and DDA as indicators of exposure to parathion. *Arch Environ Health*, 21(6):711–6. doi:10.1080/00039896.1970.10667324 PMID:5478556

Wolfe HR, Staiff DC, Armstrong JF (1978). Exposure of pesticide formulating plant workers to parathion. *Bull Environ Contam Toxicol*, 20(3):340–3. doi:10.1007/BF01683530 PMID:708924

Xu LC, Liu L, Ren XM, Zhang MR, Cong N, Xu AQ. et al. (2008). Evaluation of androgen receptor transcriptional activities of some pesticides in vitro. *Toxicology*, 243(1-2):59–65. doi:10.1016/j.tox.2007.09.028 PMID:17980950

Yousefpour M, Bahrami F, Shahsavan Behboodi B, Khoshbaten A, Asgari A (2006). Paraoxon-induced ultrastructural growth changes of rat cultured hippocampal cells in neurobasal/B27. *Toxicology*, 217(2–3):221–7. doi:10.1016/j.tox.2005.09.018 PMID:16289293

Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP. et al. (1990). A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology*, 1(5):349–56. doi:10.1097/00001648-199009000-00004 PMID:2078610

Zhang X, Wallace AD, Du P, Kibbe WA, Jafari N, Xie H, et al. (2012). DNA methylation alterations in response to pesticide exposure *in vitro*. *Environ Mol Mutagen*, 53(7):542–9. doi:10.1002/em.21718 PMID:22847954

Zurich MG, Honegger P, Schilter B, Costa LG, Monnet-Tschudi F (2004). Involvement of glial cells in the neurotoxicity of parathion and chlorpyrifos. *Toxicol Appl Pharmacol*, 201(2):97–104. doi:10.1016/j.taap.2004.05.003 PMID:15541749