Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon and Glyphosate

In March 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of organophosphate pesticides, including tetrachlorvinphos, parathion, malathion, diazinon and glyphosate (see Table). These assessments will be published as Volume 112 of the IARC Monographs (IARC).

The insecticides tetrachlorvinphos and parathion were classified as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals. Tetrachlorvinphos is banned in the European Union (EU). In the US, it continues to be used on animals, including in pet flea collars. Although excesses for non-Hodgkin lymphoma (NHL), leukemia and brain cancer were observed in the few studies that assessed tetrachlorvinphos use, the overall evidence from human studies remains inadequate. Tetrachlorvinphos induced mouse (benign or malignant) hepatocellular tumours, male mouse (benign or malignant) renal tubule tumours (Parker et al., 1985), male rat spleen haemangioma and female rat thyroid C-Cell and adrenal cortical adenomas. Tetrachlorvinphos is a reactive oxon with affinity for esterases. In experimental animals, tetrachlorvinphos is systemically distributed, metabolized, and eliminated in urine. Although bacterial mutagenesis tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and *in vitro*) and increased proliferation (hyperplasia in rodents).

Parathion has been severely restricted beginning in the 1980s, with all authorizations banned in the EU and US by 2003. The evidence for cancer in humans remains sparse, with no replication of the few cancer associations detected (including for NHL, melanoma, prostate and breast). In mice, parathion increased bronchioloalveolar tumours in males and lymphoma in females (EPA, 1991). In rats, parathion induced adrenal cortical tumours (NTP, 1979). Other rat neoplasms included (benign or malignant) pancreatic tumours and thyroid follicular cell adenomas in males, and mammary gland fibroadenomas (adenocarcinomas following subcutaneous injection during ductal morphogenesis (Cabello et al., 2011)) in females. Parathion is rapidly absorbed and distributed from the gastrointestinal tract in humans, but dermal absorption is not efficient. Parathion metabolism to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density (Cabello et al., 2001).

The insecticides malathion and diazinon were classified as Group 2A (probably carcinogenic to humans). Malathion has a wide range of uses in agriculture, and residential insect control. Malathion continues to be produced in substantial volumes throughout the world and is currently being re-registered for use in Europe. Population exposure is generally low and occurs primarily through diet, residence near sprayed areas, and home uses. There is limited evidence in humans for malathion carcinogenicity. Case-control analyses reported positive associations with NHL in the US (Waddell et al., 2001; Mills et al., 2005), Canada (McDuffie et al., 2001) and Sweden (Eriksson et al., 2008), although no NHL excesses were observed in the large Agricultural Health Study cohort (AHS). Malathion use was associated with an increased risk of prostate cancer in a Canadian case–control study and in the AHS. The AHS reported a significant trend only for aggressive cancers after adjustment for other pesticides (Koutros et al 2013a) and an effect of genetic polymorphisms related

to prostate cancer susceptibility (Koutros et al., 2013b). In rodents, malathion induced mouse (benign or malignant) hepatocellular tumours (EPA, 1994), rat thyroid carcinomas and rat hepatocellular tumours (females). Separate rat studies reported pheochromocytoma (males); occurrence of rare tumours of the nasal pharyngeal and oral cavity; and female mammary gland fibroadenoma (adenocarcinoma following subcutaneous injection during ductal morphogenesis (Cabello et al., 2001)) and uterine polyps. Malathion is rapidly absorbed and distributed following oral exposure, but dermal absorption is not efficient. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malathion induces DNA and chromosomal damage in human studies, corroborated by animal and in vitro studies. Bacterial tests were negative. Compelling evidence supports disruption of thyroid and androgen hormone pathways. Hormonal effects (rather than cytotoxicity) may mediate rodent thyroid and mammary gland proliferation. Malaoxon strongly inhibits esterases; atropine ameliorated carcinogenesis-related effects in one study (Cabello et al., 2001). Oxidative stress has been challenged experimentally.

Diazinon has been applied in agriculture and for control of home and garden insects. Production volumes have been relatively low and have reduced further since its restriction in the US and the EU. There is limited evidence in humans for the carcinogenicity of diazinon. Positive associations for NHL, with indications of an exposure-response, were reported by two large multicenter case–control studies (Waddell et al., 2001; McDuffie et al., 2001) and the AHS (Alavanja et al., 2014). Confounding by exposure to other pesticides could not explain these findings. An increased leukemia risk reported in several studies was strengthened by a monotonic increase in risk with cumulative diazinon exposure robust to adjustment for exposure to other pesticides. Multiple updates from the AHS consistently demonstrated an increased lung cancer risk with an exposure-response association, arguing against a chance finding, with no evidence of confounding by exposure to other pesticides, smoking, or other established lung cancer risk factors (Jones et al., 2015). Nonetheless, this finding was not replicated in other populations. Thus, despite positive associations and exposure-response trends for NHL, leukemia and lung cancer, there were few studies and confounding by exposure other pesticides could not be excluded. In rodents, diazinon increased mouse hepatocellular carcinoma and rat leukaemia or lymphoma (combined) incidences, but only in low dose males of each study. Diazinon induced DNA or chromosomal damage in rodents and in human and mammalian cells in vitro. Additional support for human relevance is provided by a positive study of a small number of volunteers exposed to a diazinon formulation (Hatjian et al., 2000). Oxidative stress has been challenged experimentally.

Glyphosate is currently the highest annual global production volume among herbicides (over 700 000 tonnes in 2012), with uses in over 750 different products. A broad-spectrum herbicide, glyphosate is effective against all plant types. Its use has increased sharply with the development of genetically modified glyphosate-resistant crop varieties. Glyphosate has been detected in air during spraying, in water and in food. Population exposure occurs mainly through diet. There is limited evidence in humans for the carcinogenicity of glyphosate, based on a positive association for NHL. Case-control studies in the United States (De Roos et al., 2003), Canada (McDuffie et al., 2001) and Sweden (Hardell et al., 2002; Eriksson et al., 2008) reported increased risks for NHL that persisted after adjustment for exposure to other pesticides. However, the AHS cohort did not show a significant NHL excess (De Roos et al., 2005). Observed increases in multiple myeloma were given less weight because chance and confounding by ??? could not be excluded. In male mice,

glyphosate induced a positive trend in renal tubule carcinoma, a rare tumour (EPA, 1986). A second study found increased haemangiosarcoma incidence in male mice (WHO/FAO, 2004). Two rat studies showed increased pancreatic islet cell adenoma incidence in males. A commercial formulation was a skin-tumour promoter in a mouse initiation-promotion study.

Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. In the rat, glyphosate is distributed and the plasma half-life was >1 day. Soil microbes degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection following poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induce DNA and chromosomal damage in mammals and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in community residents after spraying of glyphosate with an adjuvant or of a glyphosate formulation (Bolognesi et al., 2009). Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induce oxidative stress in rodents and in vitro. This mechanism has been challenged experimentally. Glyphosate was classified as Group 2A (probably carcinogenic to humans).

Table: Agents assessed by the Monograph 112 Working Group

Agent	**Activity (Current status)**	**Evidence in humans (Cancer Sites)**	**Evidence in animals**	**Supporting mechanistic evidence***	**Group#**
Tetrachlorvinphos	Insecticide (Banned)	Inadequate	Sufficient		2B
Parathion	Insecticide (Banned)	Inadequate	Sufficient		2B
Malathion	Insecticide (Currently used, high production volume)	Limited (NHL, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A
Diazinon	Insecticide (Banned)	Limited (NHL, leukemia, lung)	Limited	Genotoxicity and oxidative stress	2A
Glyphosate	Herbicide (Currently highest worldwide production volume	Limited (NHL)	Sufficient	Genotoxicity and oxidative stress	2A

	herbicide)				

*Strong evidence and operative in humans; #See IARC preamble for explanation of classification system

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