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 the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.1

The insecticides tetrachlorvinphos and parathion were classified as “probably carcinogenic to humans” (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the carcinogenicity of malathion. Case-control analyses of occupational exposures reported positive associations with non-Hodgkin lymphoma in the USA,2 Canada,3 and Sweden,4 although no increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS). Occupational use was associated with an increased risk of prostate cancer in a Canadian case-control study5 and in the AHS, which reported a significant trend for aggressive cancers after adjustment for other pesticides.6 In mice, malathion increased hepatocellular adenoma or carcinoma (combined).7 In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.8 Malathion is rapidly absorbed and distributed. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malaoxon strongly inhibits esterases; atropine reduced carcinogenesis-related effects in one study.9 Malathion induced DNA and chromosomal damage in humans, corroborated by studies in animals and in vitro. Bacterial mutagenesis tests were negative. Compelling evidence supported disruption of hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation.

Diazinon has been applied in agriculture and for control of home and garden insects. There was limited evidence for diazinon carcinogenicity in humans. Positive associations for non-Hodgkin lymphoma, with

<table>
<thead>
<tr>
<th>Activity (current status)</th>
<th>Evidence in humans (cancer sites)</th>
<th>Evidence in animals</th>
<th>Mechanistic evidence</th>
<th>Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrachlorvinphos</td>
<td>Insecticide (restricted in the EU and for most uses in the USA)</td>
<td>Inadequate</td>
<td>Sufficient</td>
<td>...</td>
</tr>
<tr>
<td>Parathion</td>
<td>Insecticide (restricted in the USA and EU)</td>
<td>Inadequate</td>
<td>Sufficient</td>
<td>...</td>
</tr>
<tr>
<td>Malathion</td>
<td>Insecticide (currently limited (non-commercial) use in the USA)</td>
<td>Limited (non-commercial) use in the USA</td>
<td>Sufficient</td>
<td>Genotoxicity, oxidative stress, ...</td>
</tr>
</tbody>
</table>

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indications of exposure-response trends, were reported by two large multicentre case-control studies of occupational exposures. The AHS reported positive associations with specific subtypes, which persisted after adjustment for other pesticides, but no overall increased risk of non-Hodgkin lymphoma. Support for an increased risk of leukaemia in the AHS was strengthened by a monotonic increase in risk with cumulative diazinon exposure after adjustment for other pesticides. Multiple updates from the AHS consistently showed an increased risk of lung cancer with an exposure-response association that was not explained by confounding by other pesticides, smoking, or other established lung cancer risk factors. Nonetheless, this finding was not replicated in other populations. In rodents, diazinon increased hepatocellular carcinoma in mice and leukaemia or lymphoma (combined) in rats, but only in males receiving the low dose in each study. Diazinon induced DNA chromosomal damage in rodents and in human and mammalian cells in vitro. Some additional support for human relevance was provided by a positive study of a small number of volunteers exposed to a diazinon formulation.

Diazinon is a broad-spectrum herbicide, currently with the highest production volumes of all herbicides. It is used in more than 750 different products for agriculture, forestry, urban, and home applications. Its use has increased sharply with the development of genetically modified of non-Hodgkin lymphoma. In male CD-1 mice, glyphosate induced a positive trend in the incidence of a rare tumour, renal tubule carcinoma. A second study reported a positive trend for haemangiosarcoma in male mice. Glyphosate increased pancreatic islet-cell adenoma in male rats in two studies. A glyphosate formulation promoted skin tumours in an initiation-promotion study in mice.

Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. Soil microbes degrade glyphosate to aminomethylphosphonic acid (AMPA). Blood AMPA detection after poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells in vitro. One study reported increased in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations. Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and in vitro. The Working Group classified glyphosate as “probably carcinogenic to humans” (Group 2A).

We declare no competing interests. KATHRYN Z GUYTON, DANA LOOMIS, YANN GROSSE, FATIHA EL GHISSASSI, LAMIA BENBRAHIM-TALLAO, NEELA GUHA, CHIARA SCOCCIANTI, HEIDI MATTOCK, KURT STRAIF, ON BEHALF OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER WORKING GROUP, 2017. National Toxicology Program. Bioassay of parathion for possible carcinogenicity. NCI Cancer Inst Monogr Tech Rep Ser 157(9), 701–125.


