Geneva, 9–13 May 2016 SUMMARY REPORT - *Issued 16 May 2016* - A Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR) was held at WHO Headquarters, Geneva (Switzerland), from 9 to 13 May 2016. Diazinon, glyphosate and malathion were placed on the agenda by the JMPR Secretariat, based on the recommendation of the last session of JMPR to re- evaluate these compounds given the number of new studies that had become available since their last full assessments.

The following extracts of the results of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) are provided to make them accessible to interested parties at an early date.

1. Evaluation of data for acceptable daily intake (ADI) and acute reference dose (ARfD) for humans

1.1 Diazinon (22)

Diazinon is an insecticide with a wide range of insecticidal activity. Several epidemiological studies on cancer outcomes following occupational exposure to diazinon were available. The review of these studies provided no convincing evidence of a positive association between exposure to diazinon and non-Hodgkin lymphoma (NHL), but there was weak evidence of a positive association between leukaemia and exposure to diazinon and between lung cancer and exposure to diazinon from one large cohort study only. In studies submitted, diazinon was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. Overall, these studies provided no convincing evidence of genotoxic effects, and the Meeting concluded that diazinon was unlikely to be genotoxic. The Meeting concluded that diazinon is unlikely to pose a carcinogenic risk to humans from exposure through the diet. After considering all previously evaluated data and the new studies, the Meeting established an ADI of 0–0.003 mg/kg body weight, based on inhibition of acetylcholinesterase activity as the most sensitive end-point. The Meeting reaffirmed the ARfD of 0.03 mg/kg body weight established by the 2006 JMPR based on acute (neuro)toxicity in rats.

1.2 Glyphosate (158)

Glyphosate is a broad-spectrum systemic herbicide. Several epidemiological studies on cancer outcomes following occupational exposure to glyphosate were available. The evaluation of these studies focused on the occurrence of NHL. Overall, there is some evidence of a positive association between glyphosate exposure and risk of NHL from the case–control studies and the overall meta- analysis. However, it is notable that the only large cohort study of high quality found no evidence of an association at any exposure level. Glyphosate has been extensively tested for genotoxic effects using a variety of tests in a wide range of organisms. The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2000 mg/kg body weight by the oral route, the route most relevant to human dietary exposure, was not associated with genotoxic effects in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans. The Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures. Several carcinogenicity studies in mice and rats are available. The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses. In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet. The Meeting reaffirmed the group ADI for the sum of glyphosate and its metabolites of 0–1 mg/kg body weight on the basis of effects on the salivary gland. The Meeting concluded that it was not necessary to establish an ARfD for glyphosate or its metabolites in view of its low acute toxicity.

1.3 Malathion (49)

Malathion is an insecticide used to control insects on agricultural crops and stored commodities and for vector control. Several epidemiological studies on cancer outcomes in relation to occupational exposure to malathion were available. Overall, there is some very weak evidence of a positive association between malathion exposure and NHL; however, it is notable that the only large cohort study of high quality found no evidence of an association at any exposure level. The evidence is suggestive of a positive association between occupational exposure to malathion and risk of aggressive prostate cancer; however, the evidence base is limited to the one large cohort study. The Meeting concluded that there is some evidence that malathion is carcinogenic in rats and mice. However, the formation of nasal adenomas was due to a local irritancy caused by prolonged exposure to high concentrations of malathion absorbed via inhaled food particles. Scenarios of prolonged, direct and excessive exposure of human nasal tissue to malathion or malathion metabolites following ingestion of residues is unlikely, and therefore these tumours would not occur in humans following exposure to malathion in the diet. Malathion has been extensively tested for genotoxicity, including studies in exposed workers. The Meeting noted that there are numerous reports that malathion can induce oxidative damage in cells, and these results suggest that the observed genotoxic effects occur secondary to the formation of reactive oxygen species, which will exhibit a threshold. Based on consideration of the results of animal bioassays, genotoxicity assays and epidemiological data, the Meeting

concluded that malathion and its metabolites are unlikely to pose a carcinogenic risk to humans from exposure via the diet. The current Meeting reaffirmed the ADI of 0–0.3 mg/kg body weight. The margins of exposure between this ADI and the doses causing cancer in mice and rats are 5000-fold and 1200-fold, respectively. The current Meeting also reaffirmed the ARfD of 2 mg/kg body weight. The Meeting concluded that the metabolite malaoxon is approximately 30-fold more toxic than malathion. On this basis, a 30-fold potency factor should be applied to the residue levels for use in both the acute and chronic dietary exposure estimates for malaoxon, and these should be added to the dietary exposures for malathion and compared with the ARfD and ADI for malathion, respectively.

2. General considerations

2.1 General considerations on the evaluation of genotoxicity studies

A large number of genotoxicity studies were evaluated during the present meeting. These were identified through direct submission to JMPR, searches of the publicly available literature and requests to the International Agency for Research on Cancer (IARC) Monographs Secretariat and industry groups. The studies evaluated included unpublished (primarily guideline) studies submitted to support pesticide registration as well as peer-reviewed studies published in the scientific literature. The number, quality and relevance of studies differed widely for each chemical and necessitated that a somewhat different approach be used to evaluate each pesticide. As a general strategy, the studies were separated into categories based largely on phylogenetic relevance and significance of the genetic

end-point measured. The categories used were human biomonitoring, in vivo mammals, in vitro mammalian cells, in vitro bacteria, phylogenetically distant organisms, metabolites in vivo and metabolites in vitro. The evaluation was conducted for the pesticide active ingredient, its formulation products and prominent metabolites, as data were available. For the three pesticides evaluated, the human biomonitoring studies were most often confounded by exposures to other pesticides or considered to have other limitations. Among the genotoxicity studies, in vivo studies in mammals were given the greatest weight, compared with cell culture studies or investigations in phylogenetically distant organisms. Studies of gene mutations and chromosomal alterations were also given more weight than studies measuring other less serious or transient types of genotoxic damage. With regard to route of exposure, studies in which chemicals were administered by the oral route were considered to be of most relevance for evaluating low-level dietary exposures.

Following an evaluation and weighting of the studies, taking the criteria described above and the quality of the studies into account, an overall weight of evidence approach was used to reach conclusions about the genotoxicity of the individual pesticides. An important aspect of the evaluation was whether the genotoxic effect would be likely to occur in humans exposed to low levels of the pesticide present as residues in food.

The Meeting recommended that a guidance document be developed for the evaluation of genotoxicity studies, taking the experience gained from this meeting into account.

2.2 Methods for the evaluation of epidemiological evidence for risk assessment

Identification of compound/cancer sites and screening of papers

There is a large body of literature regarding pesticide exposures and non-cancer outcomes (neurodevelopmental, neurodegenerative and reproductive outcomes, among other health outcomes), but the assessment of the epidemiological evidence on diazinon, glyphosate and malathion was restricted to studies of cancer outcomes. This restriction was partly driven by feasibility reasons: a clinically relevant adverse effect size (or an acceptable level of risk) for a non-cancer outcome must be defined, and the methodologies for hazard identification and characterization based on observational epidemiological findings of non-carcinogenic adverse effects are less well established than those for cancer.

The IARC Monographs on malathion, diazinon and glyphosate referred to a total of 45 epidemiological studies. Databases were searched for any relevant articles published after the studies cited in these Monographs using the following search terms: [(diazinon OR glyphosate OR malathion) AND cancer] and [(diazinon OR glyphosate OR malathion) AND (NHL OR lymphoma OR leukemia OR “lung cancer” OR “prostate cancer”)] in PubMed (limited to

Humans; published in the last 5 years) and Scopus (limited to 2014–2016). Two studies published since the publication of the IARC Monographs that evaluated at least one of malathion, diazinon or glyphosate were identified in relation to cancer outcomes. An additional study on prostate cancer, which was not included in the IARC Monographs, was also identified.

The pre-agreed evaluation process shown in Fig. 1 was used to (1) select compound/cancer site combinations to include in this evaluation; (2) screen papers for inclusion/exclusion in this evaluation (Tier 1 screening criteria); and (3) evaluate the information available for risk assessment. In this process, it was noted that there were stand-alone analyses for specific subtypes of non-Hodgkin lymphoma (NHL). The risk for subtypes of NHL was not evaluated separately, as there was insufficient evidence (too few studies or small numbers of cases); the risk for other haematopoietic and lymphoid tumours was also not evaluated separately, as the positive associations identified by IARC were for total NHL.

Evaluation of evidence for the compound/cancer site associations

Several aspects of each study and of all studies combined were considered in this evaluation, including factors that decrease the level of confidence in the body of evidence, such as risk of bias, unexplained inconsistency and imprecision; and factors that increase the level of confidence, such as large magnitude of effect, dose–response and consistency. The findings for each study were summarized in tables, and risk estimates for non-quantitative exposure assessment (predominantly ever versus never use) were summarized in forest plots.

Evaluation of information available for risk assessment/hazard characterization

To evaluate overall evidence for dose–response relationships, risk estimates were plotted against quantitative exposure measures (for studies that had used these). The most commonly used quantitative exposure metric was days of use per year. Where studies had used other

quantitative exposure metrics (e.g. lifetime days of exposure), data were requested from the authors on median “days of use per year” for the participants in each of the original exposure categories, although this information was not always forthcoming. These additional data allowed the translation and plotting of risk estimates from different studies on the same exposure scale (days of use per year).