Corrigenda to the *IARC Monographs* – Volume 112: Some Organophosphate Insecticides and Herbicides							
Monograph	Section	Table/Figure	Page	Details of Corrigendum	Monograph first posted online	Correction made to online version?	Correction made in printed version?
Malathion	2	2.2	29 (64 in full PDF)	The confidence interval for quartile 4 in the study by Koutros et al. (2013a) was corrected to read: "1.08 (0.9–1.29)"	21 December 2015	Yes, 5 April 2016	Yes
Malathion	3	Text Table 3.1, Table 3.3	51–65 (86–100 in full PDF)	Corrections were made to the text of section 3 and section 5.3, and tables 3.1 and 3.2, to reflect the findings of a pathology working group review (Huff et al., 1985) of the study by the NTP (1978), as detailed in "track changes" in the Appendix to the present Corrigendum (see below)	21 December 2015	Yes, 5 April 2016	Yes
	5.3	Text	105 (140 in full PDF)				
Malathion	References	Text	112–113 (147–148 in full PDF	The hyperlink for the reference EPA (1994) was updated, and the details of the reference EPA (2000b) were corrected.	21 December 2015	Yes, 5 April 2016	Yes
Diazinon	1	Fig. 1	1 (223 in full PDF)	The chemical structure of diazinon was corrected	21 December 2015	Yes, 6 June 2016	Yes

Corrigenda to the *IARC Monographs* – Volume 112: Some Organophosphate Insecticides and Herbicides							
Monograph	Section	Table/Figure	Page	Details of Corrigendum	Monograph first posted online	Correction made to online version?	Correction made in printed version?
Glyphosate	2	Table 2.1	12 (332 in full PDF)	For the study by De Roos et al (2005a), the number of exposed cases/deaths was changed to "NR" for the "Ever use" category for all the organ sites tabulated The duplicate entries for Multiple myeloma, Ever use, for this study, were also deleted	29 July 2015	Yes, 11 August 2016	Yes
Glyphosate	1.4 (b)(v)	Text	8 (328 in full PDF)	The units in the following sentence were corrected as follows: "Glyphosate concentrations in Colombia were considerably higher than in Europe, with means of 7.6 ~~ng/L~~ µg/L and 0.02 µg/L, respectively (Table 1.5)."	29 July 2015	Yes, 11 August 2016	Yes
Glyphosate	1.4	Table 1.5	10 (330 in full PDF)	For the study by Aris & Leblanc (2011), the units were corrected as follows: Arithmetic mean, 73.6 µg/L, (range, ND–93.6 ~~µg/L~~ ng/L) in nonpregnant women	29 July 2015	Yes, 11 August 2016	Yes
Glyphosate	1 and 4	Inline graphic, page 1, and Fig. 4.1	1, 43 (321 and 363 in full PDF)	Due to a technical error during updating and layout of the online document on 11 August 2016, the chemical structure of glyphosate was incorrectly replaced by the chemical structure for malathion	29 July 2015	Yes, 20 September 2016	Yes

Corrigenda to the *IARC Monographs* – Volume 112: Some Organophosphate Insecticides and Herbicides							
Monograph	Section	Table/Figure	Page	Details of Corrigendum	Monograph first posted online	Correction made to online version?	Correction made in printed version?
Parathion, and Tetrachlovinphos	4.3.2	Text	202, 440	The hyperlinks for "Annex 1" were updated in the full PDF only (not in the PDF for the individual monographs)	26 January 2017	Yes, 30 July 2018	No
Malathion	References	Text	150	The hyperlink for IARC (2015) in the list of references were corrected from: "http://monographs.iarc.fr/ENG/Monographs/vol112/112-Section4-Spreadsheet.xlsx" To: "https://monographs.iarc.fr/ENG/Monographs/vol112/112-Annex1.pdf" in the full PDF only (not in the PDF for the individual monograph)	21 December 2015	Yes, 30 July 2018	No
Annex 1	Annex 1	Text	452	The hyperlinks for the following text were updated: "http://monographs.iarc.fr/ENG/Monographs/vol112/index.php" "spreadsheet" "ToxPi software output files" In the full PDF and the individual PDF for the Annex	–	Yes, 30 July 2018	No

Appendix

Changes to section 3 and 5.3 of the *Monograph* on Malathion

3.1 Mouse

3.1.1 Oral administration

See Table 3.1

In a study by the National Cancer Institute (NCI), groups of 50 male and 50 female $B6C3F_1$ mice were given diets containing malathion (purity, ≥ 95%) at a concentration of 8000 or 16 000 ppm, respectively, for 80 weeks, and then held untreated for an additional 14–15 weeks (NTP, 1978). The matched-control group consisted of 10 male and 10 female mice. Because the number of matched-control mice was small, pooled controls were also used for statistical comparisons. The pooled-control groups consisted of the matched controls from the bioassay of malathion combined with matched controls from the contemporary bioassays of tetrachlorvinphos, toxaphene, endrin, and lindane, giving groups of 50 male and 50 female mice. There was a high percentage survival at the highest dose (males, 94%; females, 88%) compared with the matched-control groups (males, 80%; and females, 80%). Throughout the study, there was a dose-related decrease in mean body weights of males and females compared with controls.

In males, significant positive trends were noted in the incidence of hepatocellular neoplastic nodules [adenoma] (matched controls, 0/10; pooled controls, 3/49; 8000 ppm, 0/48; 16 000 ppm, 6/49; $P = 0.016$, versus matched controls) and of hepatocellular adenoma or carcinoma (combined) (matched controls, 2/10; pooled controls, 8/49; 8000 ppm, 7/48; 16 000 ppm, ~~matched controls, 2/10; pooled controls, 8000 ppm, 8/49; 16 000 ppm, 7/48;~~ 17/49; $P = 0.041$, versus matched controls). At the highest dose in male mice, there was a non-significant increase in incidence (pooled controls, 8/49 (16%); 16 000 ppm, 17/49 (35%); $P = 0.031$, which is above $P = 0.025$ level required to meet Bonferroni criterion) of these hepatocellular tumours (combined). The incidence of hepatocellular tumours (combined) was within the range for historical controls (35–40% [incidence not reported]) for that laboratory. When a time-adjusted analysis ~~(based on survival to at least 52 weeks, unless a tumour was found at the anatomical site of interest)~~ eliminated those male mice ~~that died before 52 weeks on study~~not at risk, trend values, and tumour incidence for hepatocellular tumours (combined) were non-significant when matched controls were used. There was no significant increase in the reported incidence of tumours in female mice, but an increase in the incidence of cystic endometrial hyperplasia was reported in the females in the groups receiving malathion at either dose [no statistics reported]. [The Working Group noted the low number of matched controls, that survival in the group of matched controls was lower than in the treated groups, and that the mice in this experiment were housed in the same room concurrently with mice exposed to dieldrin or tetrachlorvinphos. There were no available data on uterine weights, but the increased incidence of cystic endometrial hyperplasia pointed to a possible estrogen-like effect.]

In a second study, groups of 55 male and 55 female B6C3F$_1$ mice were given diets containing technical-grade malathion (purity, 96.4%) at a concentration of 0, 100, 800, 8000, or 16 000 ppm for 18 months (EPA, 1994, 2000b). The incidence of hepatocellular hypertrophy was significantly increased in males and females at 8000 and 16 000 ppm. The incidence of hepatocellular adenoma was significantly increased in males and females at 8000 and 16 000 ppm; statistical analysis showed a significant positive trend ($P < 0.001$) and pairwise significance ($P \leq 0.001$). In males, the incidence of hepatocellular adenoma or carcinoma (combined) had a significant positive trend ($P < 0.001$) with pairwise significance at 100 ppm ($P = 0.004$), 8000 ppm ($P < 0.001$), and 16 000 ppm ($P < 0.001$); significant increases in the incidence of hepatocellular carcinoma ($P \leq 0.014$) were reported at 100 and 8000 ppm. [The Working Group estimated that the significant increases in the incidence of hepatocellular adenoma or carcinoma (combined) reported at 8000 and 16 000 ppm in females were driven only by the incidences of hepatocellular adenoma.]

Subsequent to this study, the Environmental Protection Agency requested a re-read of the liver pathology slides for males by a pathology working group (PWG) due to the increase in the incidence of hepatocellular tumours at the lowest (100 ppm), and two higher doses (8000 ppm and 16 000 ppm), but not at the lower intermediate dose (800 ppm). Additionally, there was an apparently low incidence of tumours in the concurrent controls in this strain of mice (EPA, 1998, 2000b). Re-evaluation of the hepatocellular tumours by the PWG suggested that there was no increase in the incidence of hepatocellular tumours at 100 ppm, and no increase in the incidence of hepatocellular carcinoma in any group. In the group at 100 ppm, the PWG considered that two of the six carcinomas were in fact adenomas. In the group at 800 ppm, the study pathologist had identified two adenomas and three carcinomas, while the consensus opinion of the PWG was to upgrade all observed basophilic foci to adenomas, and to downgrade one carcinoma to adenoma, yielding seven adenomas and two carcinomas. In the group at 8000 ppm, the PWG downgraded some adenomas to eosinophilic foci, and some carcinomas to adenomas. In the group at 16 000 ppm, there was little difference between the study pathologist's interpretation and that of the PWG; adenomas (often multiple) were found in most of the animals; the study pathologist had identified one carcinoma that the PWG called adenoma (EPA, 1998). [The PWG carried out a blind review of the slides (without knowledge of the treatment received). The review resulted in a shift in the identification of adenomas versus carcinomas in favour of adenomas. The Working Group noted that the morphological appearance of most of the adenomas in animals at 16 000 ppm and the majority of those observed at 8000 ppm was quite different from that of the adenomas in the control group and in groups receiving the lower doses (100 or 800 ppm). The biological significance of this finding was not investigated in further detail. In addition, most of the hepatocellular carcinomas had been considered as single solitary masses at gross necropsy, and were diagnosed by light microscopy by the study pathologist, and multiple carcinomas were diagnosed in two mice at 100 ppm by the PWG. The Working Group highlighted the finding of hepatocellular hypertrophy and the different histological patterns identified in the groups at 8000 ppm and 16 000 ppm, the occurrence of intra-hepatic metastasizing hepatocellular carcinomas, and the polyphenotypical presentation of the histology of the hepatocellular carcinomas.]

3.1.2 Carcinogenicity of metabolites

See Table 3.2

In a 2-year study of carcinogenicity, groups of 50 male and 50 female B6C3F$_1$ mice were given diets containing malaoxon (purity > 95%), a metabolite of malathion, at a concentration of 0 (control), 500, or 1000 ppm for 103 weeks (NTP, 1979a). The mice were held untreated for up to 2 additional weeks. Mean body weight of females at the highest dose was lower than that of controls. There were no significant treatment-related changes in body weight in males. Survival at 103 weeks was 90%, 84%, and 74%, respectively, for male mice, and 78%, 76%, and 90%, respectively, for female mice. There was no significant increase in tumour incidence in groups of treated males or females. [The Working Group had minimal concerns regarding the quality of this study.]

3.2 Rat

3.2.1 Oral administration

See Table 3.3

In a first study by the NCI, groups of 50 male and 50 female Osborne-Mendel rats (age, 35 days) were given diets containing malathion (purity, 95%) at a concentration of 4700 or 8150 ppm for 80 weeks (time-weighted exposure). For matched controls (15 males and 15 females per group), the study duration was 108–113 weeks, and the study duration was 113 and 109 weeks for the lower-dose and higher-dose groups, respectively (NTP, 1978). Time-weighted doses were used to assess the results as the concentration of malathion was reduced after study start due to toxicity with initial exposures. Since the numbers of rats in the matched-control groups were small, pooled controls were also used for statistical comparisons. The pooled-control groups consisted of the matched controls from the bioassay of malathion combined with matched controls from the contemporary bioassays of tetrachlorvinphos, toxaphene, endrin, and lindane to give groups of 55 male and 55 female rats. Body weight and survival were not significantly affected by treatment. A s~~S~~ignificant positive trend~~s~~ in tumour incidence~~s were~~ was noted for ~~follicular cell carcinoma of the thyroid gland in males and females [males, $P = 0.040$; females, $P = 0.048$; compared with matched controls], and for~~ follicular cell adenoma ~~and~~ or carcinoma (combined) of the thyroid gland in females ~~($P < 0.026$~~) compared with pooled controls~~.~~~~,~~ The National Toxicology Program (NTP) in consultation with NCI re-evaluated the histopathology of the NTP (1978) study by convening a PWG, and the revised data on tumour incidence were reported by Huff *et al.* (1985). The positive trend in the incidence of follicular cell adenoma or carcinoma (combined) was no longer significant in treated females after the PWG review. ~~but T~~there were no ~~pair-wise significant~~other substantive changes in interpretation of the original data on tumour incidence ~~increases in tumour incidences over the dose groups tested~~. [The Working Group noted the low number of matched controls. The Working Group also noted that the highest dose was reduced from 12 000 ppm to 8000 ppm at 14 weeks due to excessive toxicity.] ~~The National Toxicology Program (NTP) in consultation with NCI re-evaluated the histopathology of the NTP (1978) study by convening a PWG, and the revised data on tumour incidence were reported by Huff *et al.* (1985). There were no substantive changes in interpretation of the original data on tumour incidence.~~

In a second NCI study, groups of 50 male and 49–50 female Fischer 344 rats were fed diets containing malathion (purity, 95%) at a concentration of 0 (control), 2000, or 4000 ppm for 103 weeks, and killed at 105–106 weeks (NTP, 1979a). Males, but not females, showed a dose-related decrease in body weight and survival. In males, there was a significant positive trend ($P = 0.013$) and a significant increase in the incidence of pheochromocytoma at the lower dose (controls, 2/49 (4%); lower dose, 11/48 (23%)*; higher dose, 6/49 (12%); *$P = 0.006$), and also evidence for a dose-related increase in the incidence of gastric inflammation and gastric ulcers. There was no significant treatment-related increase in the incidence of tumours in females. ~~The Working Group noted that body weights and survival of females were not significantly affected by malathion at the doses tested, and it was unlikely that the maximum tolerated dose was achieved. The Working Group had minimal other concerns with regard to the quality of this study.~~ NTP in consultation with NCI re-evaluated the histopathology of the study by convening a PWG, and the revised data on tumour incidence were reported by Huff *et al.* (1985). The positive trend and the increase in the incidence of pheochromocytoma of the adrenal gland were no longer significant in treated males after the PWG review (revised incidences: controls, 5~~3~~/49~~8~~; lower dose, 10~~2~~/48~~7~~; higher dose, 6~~3~~/46~~9~~). There were no other substantive changes in the original data on tumour incidence. [The Working Group noted that body weights and survival of females were not significantly affected by malathion at the doses tested, and it was unlikely that the maximum tolerated dose was achieved. The Working Group had minimal other concerns with regard to the quality of this study.]

In addition to the two studies described above and previously reviewed by IARC (1983), two additional studies were identified in which male and female rats were given diets containing malathion for 24 months.

Groups of 55 male and 55 female Fischer 344 rats were fed diets containing malathion (purity, 97.1%) at a concentration of 0 ppm for 24 months (control), 100 ppm for 3 months and then 50 ppm for 21 months, 500 ppm for 24 months, 6000 ppm for 24 months, or 12 000 ppm for ~~94 weeks~~24 months. Survival of male rats at 24 months was 67%, 75%, 53%, 26%, and 0%, respectively, with the majority of deaths attributed to nephrotoxicity and leukaemia. Because of excessive mortality, male rats in the group at the highest dose were killed after 94 weeks. A rare nasoturbinate adenoma (acanthoma) in a male at 6000 ppm, and another rare nasoturbinate carcinoma (malignant acanthoma) in a male at 12 000 ppm were reported (EPA, 1997, 2000b). [These nasal tumours are exceedingly rare, with a historical control rate reported by the NTP of 0.15% (6/4000) in males, and this outcome was considered to be treatment-related by the Working Group.] No other exposure-related tumours were reported in males. In the same study, survival of female rats was 69%, 74%, 75%, 62%, and 36%. Rare squamous cell carcinomas of the squamous epithelium lining the alveolus of a tooth [historical control rate: 5/1001 (0.5%), as reported by NTP (1999)] were identified in two female rats; one each was identified in the groups at 100/50 ppm and at 12 000 ppm. There were significant positive trends in the incidence of hepatocellular adenoma ($P = 0.007$), and of hepatocellular adenoma or carcinoma (combined) ($P = 0.002$), and pair-wise statistical significance at 6000 ppm ($P = 0.032$) and 12 000 ppm ($P = 0.008$) for hepatocellular adenoma, and 12 000 ppm ($P = 0.003$) for hepatocellular adenoma or carcinoma (combined). A subsequent PWG convened by the EPA (2000b) confirmed the observation of one nasal olfactory epithelium adenoma in each of the groups at 6000 ppm and 12 000 ppm, and identified one squamous cell papilloma of the palate at 100/50 ppm in males. In females, one squamous cell carcinoma of the alveolus of the tooth at 100/50 ppm was confirmed, and one nasal respiratory epithelium adenoma at 6000 ppm and one at 12 000 ppm, one squamous cell papilloma of the palate at 6000 ppm, and one squamous cell carcinoma of the palate at 12 000 ppm were identified (EPA, 1997, 2000b). [The Working Group considered that the increase in the incidence of hepatocellular tumours and the observation of squamous cell carcinomas of the oral cavity in females were treatment-related.]

In another study (EPA, 1984), groups of 50 male and 50 female Sprague-Dawley rats were given diets containing malathion (purity, 92.1%) at a concentration of 0 (control), 100, 1000, or 5000 ppm for 24 months. There was no significant effect on survival, but there was a slight decrease in body weight in treated males and females. A significant increase ($P < 0.05$) in the incidence of fibroadenoma (combined adenomas, fibromas, fibroadenomas, and papillary cystadenomas) of the mammary gland [the Working Group noted that the listed tumours are histogenetically and morphologically different] was reported in females at 1000 ppm, but not at the higher dose of 5000 ppm. [It was uncertain whether this outcome was treatment-related since there was no positive trend in tumour incidence, and the range of historical controls for this tumour was not reported for males or females.] There was no significant positive trend or increase in tumour incidence in males. [The Working Group noted that the reported incidence of fibroadenoma of the mammary gland in males at 5000 ppm – 3/47 (6.4%) – was greater than that for historical controls for Sprague-Dawley rats – 2/60 [3.3%] – as reported by Prejean *et al.* (1973).] An apparent dose-related increase in the incidence of uterine polyps was also reported in female rats [there were no available data on uterine weights, but this result suggested that malathion may have an estrogen-like effect]. [The Working Group had moderate concerns with respect to the quality of this study, including interpretation of histopathological findings.] ~~[There were no available data on uterine weights, but this result suggested that malathion may have an estrogen-like effect.]~~

3.2.2 Subcutaneous administration

See Table 3.3

Cabello *et al*. (2001) examined the effect of injection into the inguinal region of saline (control), or malathion, or malathion plus atropine, on development of the mammary gland (ductal morphogenesis) and formation of tumours of the mammary gland in groups of 70 female Sprague-Dawley rats (age, 39 days). Rats were injected with saline (subcutaneous), malathion (subcutaneous; 17 mg per 100 g body weight, bw), or malathion (subcutaneous; 17 mg per 100 g bw) plus atropine (intraperitoneal; 250 µg per 100 g bw) twice per day for 5 days and held for 28 months. Changes in body weight and survival were not reported. Rats with mammary tumours were killed 1 month after detection of the tumour by palpation. Tumours were examined by light microscopy. Tumour latency was 54–653 days. [No further information was provided on the protocol for tumour assessment, nor were data provided for individual animals.] A significant increase in the incidence of adenocarcinoma of the mammary gland (17/70, 24% [$P < 0.0001$]) was reported in the group receiving malathion only; no tumours of the mammary gland were reported in the groups receiving saline only, or malathion plus atropine. In another experiment with a similar protocol, 16 hours after the malathion injections (i.e. at age 45 days) there was an increase in terminal end bud (TEB) density and a decrease in branching to alveolar buds (ABs) compared with control animals. [TEBs and ABs represent two of the most important histogenetic milestones during the development of the normal mammary gland in rats. TEBs are club-shaped endings of secondary ducts and composed of 3–6 layers of medium-sized epithelial cells, while ABs represent further sprouting of lateral buds and cleaving of numerous TEBs. Mammary-gland differentiation is characterized by a progressive decrease in the number of TEBs and a concomitant increase in the number of ABs. The results suggested that subcutaneous injection of malathion affects ductal morphogenesis of the mammary gland in rats.]

3.2.3 Carcinogenicity of metabolites

See Table 3.4

In a 2-year study, groups of 50 male and 50 female Fischer 344 rats were given diets containing malaoxon (purity, > 95%) at a concentration of 0 (control), 500, or 1000 ppm for 103 weeks, and then held untreated for up to 2 weeks (NTP, 1979b). At 78 weeks, the rats were placed on fresh control diet for 4 days due to food rejection, before resuming the original diets. Mean body weights of males or females were not significantly affected by treatment with malaoxon. Survival at 90 weeks for male rats was 80%, 82%, and 64%, respectively. Survival at 90 weeks for female rats was 82%, 90%, and 80%, respectively. In males, there was a significant increase in the incidence of C-cell hyperplasia of the thyroid gland – 0/49, 6/45 (13%)*, 10/49 (20%)**; *[P = 0.010], **[P < 0.001] – with a significant positive trend [P < 0.001], but no treatment-related tumours were reported. In females, there was a significant pair-wise increase in the incidence of C-cell adenoma or carcinoma (combined) of the thyroid gland at the higher dose – 0/50, 1/49 (2%), 5/47* (11%); *P = 0.024 – with a significant positive dose-related trend (P = 0.009). NTP in consultation with NCI re-evaluated the histopathology of the study by convening a PWG and the revised data on tumour incidence were reported by Huff et al. (1985). There was an increase in the incidence of C-cell adenoma or carcinoma (combined) of the thyroid gland (3/49, 3/45, 10/49*; *P < 0.05) in males, with a significant positive trend (P < 0.05). There were no other substantive changes in the original data on tumour incidence.

In a 2-year study, groups of 55 male and 55 female Fischer 344 rats were given diets containing malaoxon (purity, 96.4%) at a concentration of 0 (control), 20, 1000, or 2000 ppm for 24 months (EPA, 2000b). There was a dose-related decrease in survival in males and females. In males, the increase in the incidence of mononuclear cell leukaemia was significant for the group at 1000 ppm – 13/55 (24%), 12/55 (22%), 19/55 (34%)*, 16/55 (29%); *$P < 0.05$ – with a significant positive trend ($P = 0.03$). [The Working Group noted that this type of leukaemia, commonly found in male Fischer 344 rats, may not be a suitable model for development of certain human haematopoietic neoplasms, and also that the incidences were within the range (15–36%) for historical controls for that laboratory.] There was no significant increase in tumour incidence in females.

Changes to section 5.3

5.3 Animal carcinogenicity data

Malathion was tested for carcinogenicity in two feeding studies in male and female mice and four feeding studies in male and female rats. In addition, a study in female rats examined the effect of subcutaneous injections of malathion during morphogenesis of the mammary gland. Malaoxon, a metabolite of malathion, was tested for carcinogenicity in one feeding study in male and female mice and two feeding studies in male and female rats.

Two feeding studies with malathion in male and female mice were reviewed. In the first study, malathion induced an increase in the incidence of hepatocellular adenoma with a significant positive trend in male mice. No significant increase in tumour incidence was reported in female mice. In the second study, a significant increase in the incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) with positive trends was reported in males nad females; however, there was no significant increase in the incidence of hepatocellular carcinoma only in any of the treated groups.

Four feeding studies on malathion in male and female rats were reviewed. In the first ~~study, there was a significant positive trend in the incidences of thyroid follicular cell carcinoma in males, and of thyroid follicular cell carcinoma and of thyroid follicular cell carcinoma or adenoma (combined) in females. In a~~and second studies~~y~~, no treatment-related tumours were reported in males or females. In the third study, two very rare tumours of the nasal pharyngeal cavity were identified in male rats; in addition, a rare tumour of the oral cavity was identified in two female rats. In female rats, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were ~~also~~ significantly increased with a positive trend. In the fourth study, significant increases in the incidences of fibroadenomas of the mammary gland and of uterine polyps were noted in female rats; no significant increase in the incidence of treatment-related tumours was reported in males.

Subcutaneous injection of female rats with malathion during the period of ductal morphogenesis of the mammary gland resulted in a significant increase in the incidence of adenocarcinoma of the mammary gland.

Malaoxon was evaluated for carcinogenicity in male and female mice in one feeding study; no treatment-related tumours were reported.

Two feeding studies evaluated malaoxon in male and female rats. A significant increase in the incidence of thyroid gland C-cell adenoma or carcinoma (combined) with a positive trend was reported in male and female rats in one study. In the second study in rats, there was an increase in the incidence of mononuclear cell leukaemia with a positive trend in males. This result may have been treatment related. No significant increase in tumour incidence was reported in females.

Changes to Table 3.1 and Table 3.3

Table 3.1 Studies of carcinogenicity with malathion in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, $B6C3F_1$ (M, F) 94–95 wk NTP (1978)	Diet containing malathion (technical grade; purity, ≥ 95%; dissolved in acetone) given at concentrations of 0 (matched control), 0 (pooled control), 8000, or 16 000 ppm, ad libitum, 7 days/wk, for 80 wk, then held untreated for an additional 14–15 wk 50 M and 50 F~~-~~/treated group; 10 M and 10 F/matched-control group (age, 35 days) Since the numbers of mice in the matched-control groups were small, statistical comparisons also made use of pooled-control groups, which consisted of matched controls from the malathion bioassay combined with matched controls from contemporary bioassays of tetrachlorvinphos, toxaphene, endrin, and lindane, resulting in groups of 50 M and 50 F	*Males* Hepatocellular neoplastic nodule [adenoma]: 0/10, 3/49 (6%), 0/48, 6/49 (12%) Hepatocellular carcinoma: 2/10 (20%), 5/49 (10%), 7/48 (15%), 11/49 (22%) Hepatocellular adenoma or carcinoma (combined): 2/10 (20%), 8/49 (16%), 7/48 (15%), 17/49 (35%)* Hepatocellular adenoma or carcinoma (combined) (time-adjusted): 2/9 (22%), 8/48 (17%), 7/47 (15%), 17/49 (35%) *Females* No exposure-related tumours	*Males* Neoplastic nodule [adenoma]: $P = 0.016$ (trend) (vs matched) Adenoma or carcinoma (combined): $P = 0.041$ (trend) (vs matched); time-adjusted analysis, eliminating mice ~~that died at < 52 wk of exposure unless a tumour was found~~not at risk.~~-~~ NS for trend and pairwise comparison to matched control group *$P = 0.031$ (vs pooled) *Females* NS	There was a dose-related decrease in mean body weights compared with controls. Low number of matched controls. Mice fed malathion were housed in the same room as mice fed dieldrin or tetrachlovinphos *Males* No significant dose-related trend in mortality: survival was 94% at higher dose, 80% in matched-control group. Historical control rate for hepatocellular carcinoma in males in the laboratory was 35–40% (incidence, NR) *Females* No significant dose-related trend in mortality: survival was 88% at higher dose; 80% in matched-control group Cystic endometrial hyperplasia: 1/9 (11%), 12/47 (25%), 10/42 (24%) Cystic endometrial hyperplasia is a potential estrogenic effect of the exposure; values for pooled controls, NR
Mouse,	Diets containing malathion (purity, 96.4%) given at	*Males*		Significant reduction in body weight at

Table 3.1 Studies of carcinogenicity with malathion in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
$B6C3F_1$ BR (M, F) 18 mo EPA (1994, 2000b)	concentrations of 0 (control), 100, 800, 8000, or 16 000 ppm, ad libitum, 7 days/wk, for 18 mo 55 M and 55 F/group [age NR]	Hepatocellular adenoma: 1/54 (2%), 6/54 (11%), 2/55 (4%), 13/55 (24%)*, 49/51 (96%)* Hepatocellular carcinoma: 0/54, 6/54 (11%)*, 3/55 (5%), 6/55 (11%)*, 1/51 (2%) Hepatocellular adenoma or carcinoma (combined): 1/54 (2%), 10/54 (19%)*~~**~~, 5/55 (9%), 18/55 (33%)*~~*~~, 49/51 (96%)*~~*~~ ~~Pathology Working Group re-read (EPA, 1998, 2000b)~~ ~~Hepatocellular adenoma:~~ ~~4/54 (7%)*, 8/54 (15%), 7/55 (13%), 14/55 (25%)**, 49/51 (96%)**~~ ~~Hepatocellular carcinoma:~~ ~~0/54, 4/54 (7%), 2/55 (5%), 2/55 (4%), 0/51~~ ~~Hepatocellular adenoma or carcinoma (combined):~~	Adenoma: *$P \leq 0.001$, Fisher exact test; $P < 0.001$, trend test Carcinoma: *$P \leq 0.014$, Fisher exact test Adenoma or carcinoma (combined): ~~*~~$P = 0.004$, Fisher exact test; **$P < 0.001$, Fisher exact test~~;***$P = 0.004$, Fisher exact test~~; $P < 0.001$, trend test ~~*$P < 0.001$ (trend test)~~ ~~**$P \leq 0.01$ (Fisher exact test)~~	78 wk; 48–54 mice per group at terminal kill; two higher doses chosen to duplicate NTP (1978) study; liver hypertrophy at 12 mo in two highest dose groups Hepatocellular hypertrophy: 0/54, 0/55, 0/55, 55/55*, 51/51*; [hepatocellular hypertrophy, *$P < 0.001$, $P < 0.001$ (trend)] Historical controls: hepatocellular adenoma, 14.3–21.7%; hepatocellular carcinoma, 0.0–6.4%

Table 3.1 Studies of carcinogenicity with malathion in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
		~~4/54 (7%)*, 10/54 (19%), 9/55 (16%), 15/55 (27%)**, 49/51 (96%)**~~		
		Pathology Working Group re-read (EPA, 1998, 2000b) Hepatocellular adenoma: 4/54 (7%)*, 8/54 (15%), 7/55 (13%), 14/55 (25%)**, 49/51 (96%)** Hepatocellular carcinoma: 0/54, 4/54 (7%), 2/55 (5%), 2/55 (4%), 0/51 Hepatocellular adenoma or carcinoma (combined): 4/54 (7%)*, 10/54 (19%), 9/55 (16%), 15/55 (27%)**, 49/51 (96%)**	*$P < 0.001$, trend test **$P \leq 0.01$, Fisher exact test	

Table 3.1 Studies of carcinogenicity with malathion in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
		Females Hepatocellular adenoma: 0/55, 1/53 (2%), 0/53, 9/52 (17%)*, 42/51 (82%)* Hepatocellular carcinoma: 1/55 (2%), 0/53, 2/53 (4%), 1/52 (2%), 2/51 (4%) Hepatocellular adenoma or carcinoma (combined): 1/55 (2%), 1/53 (2%), 2/53 (4%), 10/52 (19%)*, 43/51 (84%)**	Adenoma: *$P \leq 0.001$, Fisher exact test; $P < 0.001$, trend test Adenoma or carcinoma (combined): *$P = 0.003$; **$P < 0.001$, ~~*$P = 0.003$ (~~Fisher exact test~~)~~; $P < 0.001$, trend test	Significant reduction in body weight at 78 wk 51–55 mice/group at terminal kill Two highest doses chosen to duplicate NTP (1978) study; liver hypertrophy at 12 mo in two highest dose groups Hepatocellular hypertrophy: 0/55, 0/55, 0/54, 53/53*, 52/52*; [hepatocellular hypertrophy, *$P < 0.001$, $P < 0.001$ (trend)] Historical controls: hepatocellular adenoma, 0.0–10.6%; hepatocellular carcinoma, 0.0–2.3%

F, female; M, male; mo, month; NR, not reported; NS, not significant; vs, versus; wk, week

Table 3.3 Studies of carcinogenicity with malathion in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat,	Diets containing malathion (purity, ≥ 95%;	*Males:*	*Males*	*Males*

Table 3.3 Studies of carcinogenicity with malathion in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Osborne Mendel (M, F) 108–113 wk NTP (1978): Huff *et al.* (1885)	dissolved in acetone) at concentrations of 0 (matched control), 0 (pooled control), 4700 ppm (time-weighted average: 14 wk at 8000 ppm then 66 wk at 4000 ppm), and 8150 ppm (time weighted average: 3 wk at 12 000 ppm and then 77 wk at 8000 ppm) Fed ad libitum, 7 days/wk for 80 wk, and rats then held untreated for an additional 28–33 wk 50 M and 50 F/treated group (age, 35 days); 15 M and 15 F/matched-control group Since the numbers of rats in the matched-control groups were small, statistical comparisons also made use of pooled-control groups, which consisted of matched controls from the malathion bioassay combined with matched controls from contemporary bioassays of tetrachlorvinphos, toxaphene, endrin, and lindane, resulting in 55 M and 55 F/group	Thyroid gland: C-cell adenoma: 1/14 (7%), 3/41 (7%), 1/35 (3%), 7/40 (18%)~~0/14, 2/46 (4%) (pooled controls), 1/41 (2%), 3/47 (6%)~~ Follicular cell adenoma: 1/14 (7%), 6/41 (15%), 7/35 (20%), 8/40 (20%) ~~1/14 (17%), 1/41 (2%), 1/47 (2%); [pooled-control values, NR]~~ Follicular cell carcinoma: 1/14 (7%), 2/41 (5%), 2/35 (6%), 4/40 (10%)~~0/14, 2/41 (5%), 6/47 (13%); [pooled-control values, NR]~~ ~~Follicular cell adenoma or carcinoma (combined): 1/14 (17%), 4/46 (9%) (pooled controls), 3/41 (7%), 7/47 (15%)~~ *Females* Thyroid gland: C-cell adenoma: 2/14 (14%), 9/41 (22%), 2/44 (5%), 4/42 (10%) ~~0/15, 1/46 (2%) (pooled controls), 1/48 (2%), 2/49 (4%)~~ Follicular cell adenoma: 0/14, 1/41 (2%), 1/44 (2%), 1/42 (2%) ~~0/15, 0/46 (pooled controls), 0/48, 1/49 (2%)~~ Follicular cell carcinoma: 0/14, 0/41, 0/44, 3/42 (7%)~~0/15, 0/46 (pooled controls), 0/48, 3/49 (6%)~~	~~[Follicular cell carcinoma; $P = 0.040$ (trend) vs matched controls, Cochran-Armitage]~~NS *Females* ~~[Follicular cell carcinoma; $P = 0.048$ (trend) vs matched controls, Cochran-Armitage]~~ ~~Follicular cell adenoma or carcinoma (combined); $P < 0.026$ (trend) vs pooled controls, Cochran-Armitage~~NS	Body weight and survival not significantly affected; survival at highest dose, 58% ~~Thyroid gland~~ ~~C-cell hyperplasia: 0/14, 1/41 (2%), 3/47 (6%); [pooled-control values, NR]~~ Follicular cell hyperplasia: 1/14 (7%), 7/41 (17%), 8/47 (17%); [pooled-control values, NR] Low number of matched controls housed together with dosed rats; pooled controls included rats on test as controls for four other chemicals *Females* Body weight and survival not significantly affected; survival at highest dose, 67% ~~Thyroid gland~~ ~~C-cell hyperplasia: 0/15, 5/48 (10%), 3/49 (6%); [pooled-control values, NR]~~ ~~Follicular cell hyperplasia: 0/15, 3/48 (6%), 0/49 [pooled-control values, NR]~~ Low number of matched controls housed together with dosed rats; pooled controls included rats on test as controls for four other chemicals

Table 3.3 Studies of carcinogenicity with malathion in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
		~~Follicular cell adenoma or carcinoma (combined): 0/15, 0/46 (pooled controls), 0/48, 4/49 (8%)~~		NTP in consultation with NCI re-evaluated the histopathology of the study by convening a PWG and the tumour incidence data were reported by Huff *et al.* (1985).
Rat, F344 (M, F) 105–106 wk NTP (1979a)	Diets containing malathion (purity, 95%; dissolved in acetone) at 0 (control), 2000, or 4000 ppm, fed ad libitum, 7 days/wk for 103 wk and rats then held untreated for an additional 2–3 wk 49–50 M and 50 F/group (age, 35 days)	*Males* Pheochromocytoma of the adrenal gland: 2/49 (4%), 11/48 (23%)*, 6/49 (12%)	*Males* *P = 0.006, Fisher exact test (see Comments) P = 0.013 (trend), Cochran-Armitage test (see Comments)	*Males* Dose-related decrease in body weight Survival at 78 wk: controls, 88%; lower dose, 86%; higher dose, 80% Stomach: chronic inflammation: 2/49, 6/46, 11/47; gastric ulcers: 1/49, 9/46, 15/47
		Females No exposure-related tumours	*Females* NS	*Females* Body weight not significantly affected. Survival at 78 wk: controls, 94%; lower dose, 98%; higher dose, 90%. Individual clinical signs of toxicity were not reported, but it is unlikely that the MTD was achieved Stomach: chronic inflammation: 0/50, 2/44, 4/47; gastric ulcers: 1/50, 2/44, 2/47 NTP in consultation with NCI re-evaluated the histopathology of the study by convening a PWG and the tumour incidence data were reported by Huff *et al.* (1985). The positive trend and the increase in the incidence of pheochromocytoma of the adrenal gland (~~5~~3/49~~8~~, 10~~2~~/48~~7~~, ~~6~~3/46~~9~~) were no longer significant for males. There were no other substantive changes in the original data on tumour incidence

Table 3.3 Studies of carcinogenicity with malathion in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) Up to 24 mo EPA (1997, 2000b)	Diets containing malathion (purity, 97.1%) at 0 ppm for 24 mo (control), 100 ppm for 3 mo then 50 ppm for 21 mo, 500 ppm for 24 mo, 6000 ppm for 24 mo, or 12 000 ppm for ~~94 wk~~24 mo Fed ad libitum, 7 days/wk for up to 24 mo 55 M and 55 F/group [age NR]	*Males* Nasal pharyngeal cavity: one very rare adenoma (acanthoma) at 6000 ppm, and one very rare carcinoma (malignant acanthoma) at 12 000 ppm in nasoturbinate tissues, olfactory region. These tumours originated in the stratum spinosum layer of the epithelium	*Males* (see Comments)	*Males* Survival at 24 mo: 67%, 75%, 53%, 26%, 0%; most deaths due to nephrotoxicity and leukaemia Nasal tumours are exceedingly rare, with a historical control rate (NTP) of 6/4000 (0.15%) *Males* Group at highest dose was terminated at 94 wk because of excessive mortality PWG re-read (EPA, 2000b): Males: one nasal olfactory epithelium adenoma at 6000 ppm, one nasal respiratory epithelium adenoma at 12 000 ppm, and one squamous cell papilloma of the palate at 100/50 ppm
		Females Oral cavity: rare squamous cell carcinoma of the squamous epithelium lining of the alveolus of a tooth was identified in two females; one at 100/50 ppm and one at 12 000 ppm Liver: Hepatocellular adenoma: 0/40, 1/48 (2%), 1/43 (2%), 3/39 (8%)*, 3/29 (10%)** Hepatocellular carcinoma: 0/41, 1/50	*Females* Peto's prevalence test Hepatocellular adenoma: $P = 0.007$ (trend), $*P = 0.032$ (6000 ppm), $**P = 0.008$ (12 000 ppm) Hepatocellular adenoma or carcinoma (combined): $P = 0.002$ (trend), $*P = 0.032$	*Females* Survival at 24 mo: 69%, 74%, 75%, 62%, 36% Historical controls (NTP, 1999): squamous-cell carcinoma of the oral cavity, 5/1001 (0.5%) Historical controls (NTP): hepatocellular adenoma, 8/1351 (0.59%); hepatocellular carcinoma, 1/1351 (0.07%) PWG re-read (EPA, 2000b): Females: one nasal respiratory epithelium adenoma at 6000 and one at 12 000 ppm, one squamous cell

Table 3.3 Studies of carcinogenicity with malathion in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
		(2%), 1/44 (2%), 0/41, 3/38 (8%) Hepatocellular adenoma or carcinoma (combined): 0/41, 2/50 (4%), 2/44 (5%), 3/41 (7%)*, 6/38 (16%)**	(6000 ppm), **P = 0.003 (12 000 ppm)	papilloma of the palate at 6000 ppm, one squamous cell carcinoma of the palate at 12 000 ppm, and one squamous cell carcinoma of the alveolus of the tooth at 100/50 ppm