

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**TOXICOLOGICAL DATA ON SPECIFIC CHEMICALS IDENTIFIED
THROUGH THE REVIEW EXTRACTED FROM THE EU REGULATORY
DRAFT ASSESSMENT REPORTS (DARs) BY THE CHEMICALS
REGULATION DIRECTORATE (CRD)**

Captan - Carcinogenicity

1. In a 2-year toxicity and carcinogenicity study in the rat, body weight was reduced in 100 and 250 mg/kg bw/day treatment groups compared to the control. Increases in mean absolute and relative liver and kidney weights were observed at the 18 month sacrifice in 250 mg/kg/day males and this was related to the significant hepatocellular hypertrophy of a centrilobular, focal, multifocal or diffuse nature observed microscopically in this group. This lesion was present in all ten males and eight of the ten females, compared to zero incidence in other treatment groups and the controls. No microscopic changes were noted in the kidney. The incidence of microscopic neoplastic and non-neoplastic lesions was comparable between treatment groups and the controls. There was no statistically or toxicologically significant increase in any tumour type, total tumours, total benign tumours or total malignant tumours.

2. In another life-span toxicity study in the rat, body weight was decreased throughout the study in 2,000 ppm males and females. Food consumption was reduced compared to the controls in this group during the first two years of the study, but was similar to control levels towards the end of the study. Food efficiency was initially reduced in the 2,000 ppm dose group males and females. There were no treatment-related increases in the incidence of hyperplastic or pre-neoplastic lesions in treatment groups compared to the control. There was no significant difference between treatment groups and controls in the incidence of any tumour types and no relationship between dose and tumour incidence. No association between the occurrence of tumours and the presence of hyperplastic or pre-neoplastic changes was apparent.

3. In a study carried out to investigate the oncogenicity of captan in mice, a significantly higher incidence in mortality was observed in 16,000 ppm males. Body weights and food consumption were significantly reduced in all dose groups during the study. There was a positive correlation between the administration of captan and the incidence of duodenal adenomas and adenocarcinomas in males and females and a negative correlation with the incidence of lung and liver tumours.

4. In another life-span oncogenicity study in the mouse, mortality was increased in the 6,000 ppm dose group males during the first 14-months of

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the study. Mortality in females was comparable to the controls. Pronounced alopecia was noted in 6,000 ppm males and females from the first month of treatment. Body weights in 100, 400 and 800 ppm males were reduced initially and in 6,000 ppm males and females throughout the study. Food consumption by males was increased during the first few months of the study. The results of the gross postmortem revealed an increase in the incidence of lesions of the small intestine (masses, nodules, raised areas) in female mice from the 800 and 6,000 ppm groups. Microscopic examination revealed an increased incidence of small intestinal proliferative (non-neoplastic and neoplastic) lesions. The incidence of duodenal hyperplasia was higher in 6,000 ppm males and females. The number of animals with benign and malignant duodenal neoplasms was also increased in the high dose group animals. These lesions are considered rare in the mouse. The incidence of benign duodenal neoplasms in 100 ppm males was 3 out of 79. The distribution and incidence of benign and malignant neoplasms that developed in various other organs and tissues were similar to the control, bearing no obvious relation to treatment. There was no treatment-related effect on the incidence of non-neoplastic lesions.

5. In a later study, the duodenal tissues from the above mouse study were re-evaluated. It was concluded that there was an increase in benign neoplasms (adenoma and adenoma with atypia) in 800 and 6,000 ppm females and possibly in 6,000 ppm males, and adenocarcinoma was increased in 6,000 ppm males and females. Although adenoma was present in control males and females, adenocarcinoma was absent from these groups. Focal mucosal hyperplasia was increased in 6,000 ppm males and females. Lymphoid proliferation was more prominent in 6,000 ppm males and 800 and 6,000 ppm females. Amyloidosis was high in all groups. There were no significant differences in the incidence of proliferative and non-proliferative lesions between the 100 and 400 ppm dose groups and the controls. On the basis of an increased incidence of malignant and/or benign neoplasm of duodenal crypt cells in females at 800 ppm, and both sexes at 6,000 ppm, the non-tumourigenic dose in this study is 400 ppm (equivalent to 61 mg/kg bw/day).

Chlorpyrifos – Carcinogenicity

6. No tumourigenic or carcinogenic effect was seen in rats or mice at chlorpyrifos dosages up to 10 mg/kg bw/day and 47.1 (males) to 50.2 (females) mg/kg bw/day, respectively.

7. The 2-year chronic dietary NOAEL in Fischer 344 rats was 0.3 mg/kg bw/day based on decreased body weight gain (and erythrocyte cholinesterase inhibition) at 1 mg/kg bw/day.

8. The NOAEL in CD-1 mice after 18 months' treatment was 0.9 - 1.0 mg/kg bw/day based on reduced brain cholinesterase activity and/or ocular effects at higher dosages (\geq 9.2 mg/kg bw/day).

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9. In a 2-year dietary study in dogs, the NOAEL was 1.0 mg/kg bw/day based on reduced brain cholinesterase at 3.0 mg/kg bw/day.

10. In the long-term studies there were no increases in any tumours mentioned and written-off.

Picloram - Carcinogenicity

11. The chronic toxicity and carcinogenicity of picloram was investigated in two rat studies and one mouse study submitted by the Notifier. The carcinogenicity of picloram has additionally been investigated in two NTP studies in the rat and mouse, which are summarised below.

12. A NOAEL could not be determined for the study of Cosse *et al* (1992) due to the increased severity of chronic glomerulonephropathy in males at the low dose level of 250 mg/kg bw/d; renal findings in high dose level males included cysts and papillary necrosis. Renal findings in females in this study were less marked and were limited to increased organ weight and an increased severity of chronic glomerulonephropathy at the top dose level. Liver findings were limited to centrilobular hepatocyte hypertrophy and eosinophilia at the interim sacrifice. Changes in clinical chemistry parameters in this study were consistent with liver toxicity in both sexes and kidney toxicity in males. Some evidence of carcinogenicity was seen in this study, with a slightly increased incidence of hepatocellular adenoma in top dose females. Evidence of an effect on red blood cell parameters was seen in this study, however effects were only seen at 6 months in males; similar findings were not apparent in the other rat study (Landry *et al*, 1986). In the study of Cosse *et al* (1992), total white blood cell counts were markedly higher in both sexes at 200 mg/kg bw/d and in 60 mg/kg bw/d females; values did not attain statistical significance due to high variability and are not associated with any significant effects on the differential count, similar effects were not seen in the other rat study (Landry *et al*, 1986) even at higher doses. A NOAEL of 60 mg/kg bw/d was determined for this study, based on increased liver weights, haematology and clinical chemistry at the top dose level of 200 mg/kg bw/d. No evidence of carcinogenicity was seen in this study, however the dose levels investigated are lower than that causing an increase in liver adenomas in the other rat study. The NTP study of picloram in rats (summarised below) also noted an increased incidence of benign liver tumours in female rats at the top dose level.

13. Two bioassays (reported in 1978) with picloram were performed by the US National Toxicology Program (NTP). In one study, Osborne-Mendel rats (50/sex/group) were administered picloram in the diet at time-weighted average dose levels of 7437 or 14875 ppm for 80 weeks; animals were terminated at 113 weeks. A relatively high incidence of thyroid follicular hyperplasia, C-cell hyperplasia and C-cell adenoma are reported in both sexes; statistical tests for adenoma are stated not to provide sufficient evidence of an association with picloram treatment. An increased incidence of hepatic neoplastic nodules was observed in treated males and females,

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compared to pooled controls, with a positive dose-related trend seen in females.

14. In an additional study, B6C3F1 mice (50/sex/group) were administered picloram in the diet at time-weighted average dose levels of 2531 or 5062 ppm for 70 weeks; animals were terminated at 80 weeks. No evidence of tumorigenicity was seen in this study

Chlorothalonil - Carcinogenicity

15. Six chronic toxicity/carcinogenicity studies were considered for the EU review. The most critical effects of chlorothalonil observed in rats as well as in mice were changes in absolute and relative kidney weights, and pathology of kidneys and the gastrointestinal tract, especially the forestomach. The pathology included pre-neoplastic and neoplastic lesions. In addition, effects on haematology (red blood cell parameters) were observed in mice and effects on urine composition and clinical chemistry (both not determined in mice) were observed in rats.

16. The most sensitive toxicological endpoints in the chronic studies with rats were kidney and forestomach morphology. In mice, the most sensitive endpoint was pathology of the forestomach. In two studies with rats, all dose levels exhibited systemic toxicity. In one with rats the LOAEL was 40 mg/kg bw/day (one study with lower doses was inappropriate for evaluation of systemic toxicity). In another study in rats, the lowest dose with histopathological effects on the target organs (pre-neoplastic lesions in kidneys and forestomach and benign tumours in the forestomach) was 3.8 mg/kg bw/day.

17. In a 104-week study in rats, a NOAEL of 0.7 mg/kg bw/day was established for local effects, based on (histo)pathological changes in the stomach. Based on histopathological changes in liver and kidneys, and effects on haematology, a NOAEL for systemic effects was established at 2.7 mg/kg bw/day.

18. In chronic toxicity and carcinogenicity study in mice, the lowest dose tested, 119 mg/kg bw/day, still revealed an increased incidence of pre-neoplastic lesions in the forestomach. In a second study in male mice only (as the most sensitive gender) and a limited set of parameters tested, no effects were observed at 1.9 mg/kg bw/day. A positive tumour response was observed in the forestomach at 99.7 mg/kg bw/day. No increased incidences in tumours were observed at 23.2 mg/kg bw/day.

19. In an 80-week oral carcinogenicity study in mice, an increased incidence of non-neoplastic lesions in the stomach was still observed in the lowest dose level of 1.9 mg/kg bw/day. Based on these findings, a NOAEL for local effects was established at < 1.9 mg/kg bw/day. Based on the observed histopathological findings in the kidneys, a NOAEL of 1.9 mg/kg bw/day was established for systemic effects. At the highest dose (130 mg/kg bw/day) a

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statistically significant increase in squamous cell papilloma in the non-glandular stomach of both sexes was observed.

Glyphosate - Carcinogenicity

20. Five long term studies in rats and four in the mouse were considered in the EU review

21. In the rat there were no adverse effects on survival and no clinical signs of toxicity. There were some effects on bodyweight gain in females at the top dose level tested. There was evidence of a slight effect on the liver (serum chemistry and increased liver weights)). Effects on the eyes (cataracts) and salivary glands (cellular alteration in the parotid and mandibular gland and increased weights of these glands) were reported. Local effects on the gastric mucosa were reported also well as epithelial hyperplasia in the urinary bladder.

22. In the mouse, at high doses there was some evidence for reduced bodyweight gain. In high dose males, hepatocyte hypertrophy and epithelial hyperplasia in the urinary bladder. There were some equivocal effects; increased thymus weight and mineral deposits in the brain.

Secretariat

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