CHLORDIMEFORM

Explanation

Chlordimeform was reviewed and evaluated for an Acceptable Daily Intake in 1971, 1975, 1978, and 1979 (FAO/WHO, 1972, 1976; FAO, 1979, 1980). In 1971, a temporary ADI was allocated. In 1976, as a result of long-term studies in mice, which showed a potential carcinogenic response characterised histologically as hemangioendothelioma, the distribution of chlordimeform was voluntarily and temporarily suspended. In 1978, an extensive series of short-term, high-level, and long-term, low-level studies in both rats and mice were reviewed. Results of long-term studies demonstrated that chlordimeform and its principal metabolites, N-formyl-4-chloro-o-toluidine, and 4-chloro-o-toluidine, were carcinogenic in the mouse, producing a dose-related malignant hemangioendothelioma in various tissues. Carcinogenicity studies with these compounds in rats, predominantly negative, were somewhat conflicting. Chlordimeform itself was not mutagenic to bacteria but the 4-chloro-o-toluidine, the major metabolite, was mutagenic. The temporary ADI was maintained at a reduced level in the light of the new information and with the consideration that further long-term studies were in progress. In 1979, complete results of long-term studies in rats and mice with 4-chloro-o-toluidine and in rats with chlordimeform were submitted in detail to the Meeting and were reviewed. Interim reports of chronic toxicity studies in rats administered 4-chloro-o-toluidine and N-formyl-4-chloro-o-toluidine were reviewed. Additionally, pharmacokinetic data and mutagenicity studies were reviewed. In these
studies, there was no evidence for bioaccumulation or unusual metabolite formation. The data further suggested a lack of mutagenic potential in mammalian systems. A complete review of the data was not performed in anticipation of submission of completed studies in time for the 1980 Meeting.

Complete results of the two-year studies with chlordimeform and its two principal metabolites in rats have been submitted in detail. In addition, short-term, high-level dietary studies in rats and mice administered chlordimeform or the N-formyl metabolite were made available and reviewed. This monograph addendum includes that new information received and does not constitute a full review of the toxicology of chlordimeform.

DATA CONSIDERED FOR DERIVATION OF ACCEPTABLE DAILY INTAKE

TOXICOLOGICAL STUDIES

Short-term studies

Rats

Groups of rats (30 males and 30 females/group), housed under SPF conditions, were fed chlordimeform in the diet at dosage levels of 0, 750, 1,500, 3,000 or 6,000 mg/kg for 60 days. These dosage levels corresponded to dietary intakes of 0, 84, 137, 222, or 462 mg/kg bw/day for males and 0, 71, 121, 231 or 464 mg/kg bw/day for females.

Groups of 10 males and 10 females were sacrificed at 60 days for complete haematological, clinical chemistry, and urinalysis examinations. At the end of the study, 10 males and 10 females from each group were subjected to gross and microscopic pathological examination as well all animals that died over the course of the study.

Food intake and growth were reduced over the course of the study, at all dose levels. Slight mortality was observed at the highest concentration. Clinical signs of toxicity or adverse behaviour were not noted at any dose level. Slight changes in several haematological parameters were noted at the two highest dose levels. Methaemoglobin levels were increased in a dose-related manner at all treatment levels. Heinz bodies were noted in haematologic examination at 1,500 mg/kg and above. Slight changes were noted in several clinical chemistry parameters including: decreased glucose concentration, increased alkaline phosphatase activity, and increased gamma-glutamyl transpeptidase activity, predominantly at the three highest dose levels. Urinalyses showed slight changes at the two highest dose levels including a reduced urine volume, reduced protein concentration, and reduced electrolyte (potassium) level, predominantly at the highest dietary levels.

Terminal body weights of all animals administered chlordimeform were significantly reduced in a dose-related fashion. Substantial changes in growth and relative organ weights were noted in both males and females at all dietary levels. Reductions in the weight of such organs as the brain, heart, liver, kidneys, adrenals, and thymus were
reported for both males and females. In males, reduced testes weight was noted only at the highest dose level while reduced ovarian weights were noted at all dose levels.

Other than excessive emaciation at the highest dose level, no gross anatomical changes were noted in the animals sacrificed for pathological examination. In most rats of the highest dose groups, haemosiderosis in the spleen was observed. Reduced spermatogenesis was noted at the highest concentration. Focal hyperplasia of small biliary ducts and of the transitional epithelium and increased vascularisation in the mucous membrane of the bladder was observed in the highest dose group. In addition, the highest dose group showed thymic atrophy in several of the animals examined. No compound-related histopathological changes were noted in rats treated with 1,500 mg/kg or below (Sachsse et al., 1979a).

Groups of rats (30 males and 30 females/group), housed under SPF conditions, were fed N-formyl-4-chloro-o-toluidine in the diet at dosage levels of 0, 750, 1,500, 3,000 or 6,000 mg/kg for 60 days. These dosage levels corresponded to dietary intakes of 0, 91, 176, 347 or 875 mg/kg bw/day for males and of 87, 165, 329 or 719 mg/kg bw/day for females. Groups of 10 males and 10 females were sacrificed at the conclusion of the study for complete haematological clinical chemistry, urinalysis examinations, and gross and microscopic pathological examinations of tissues and organs.

Extensive mortality was observed at the high dose level within the first few weeks of the experiment. At the end of the third week of treatment, the highest dose level was terminated. There was no substantial mortality at dose levels of 3,000 mg/kg and below. Food intake and growth were reduced over the course of the study in a dose-dependent fashion in all dose groups. Other than mortality noted at the high dose level, no clinical signs of toxicity or adverse behaviour were observed. Auditory and ophthalmological examinations showed no evidence of loss of these functions in any of the animals examined.

The results of the haematologic examination suggested a toxic haemolytic anemia in both sexes of all treatment groups; characterised by reduction of haemoglobin concentration, erythrocyte count, packed cell volume and an increase in methaemoglobin. Heinz bodies were observed at 3,000 mg/kg. In addition, at 1,500 mg/kg and above there was a slight reticulocytosis and reduced partial thromboplastin time in these dose groups. Changes in the clinical chemistry parameters were noted at both 1,500 and 3,000 mg/kg.

Gross examination of certain tissues and organs showed changes in absolute weights and relative weight ratios at all dosage levels. These reductions appeared to follow a dose-dependent relationship. Animals administered 6,000 mg/kg showed atrophy of the thymus and spleen within the first three weeks of the test. Liver changes were noted in all dose groups characterised as hyperplasia of the bile duct epithelium and changes in the distribution of lipid. At the highest dose group, hyperplasia of the urinary bladder epithelium and testes was noted. About half the animals of both sexes in the 6,000 mg/kg group showed an increase in the mitotic incidence in hepatocytes.
Mice

Groups of mice (30 male and 30 female mice/group), housed under SPF conditions, were fed chlordimeform in the diet at dosage levels of 0, 750, 1,500, 3,000, or 6,000 mg/kg for 60 days. These dosage levels corresponded to dietary intakes of 0, 107, 194, 616, or 1,525 mg/kg bw/day for females and 0, 119, 200, 669, or 1,519 mg/kg bw/day for males. At the end of the 60-day interval, all animals were examined for haematologic, blood chemistry, and urinalysis parameters. At the conclusion of the study, groups of 10 male and 10 female animals from the control and the lower three dose groups, maintained for 60 days, were subjected to gross and microscopic examination of tissues and organs.

Mortality was observed in the two highest dose groups over the course of the study. The 6,000 mg/kg dose group was terminated after two weeks because of a general poor condition. Growth, as evidenced by body weight gain, was reduced in all dietary groups. Food consumption was reduced in females only over the course of the study at all dietary levels. No clinical signs of toxicity were noted. Ophthalmologic and auditory examinations were normal. The results of haematological investigations showed a toxic haemolytic anaemia observed in both sexes of all treated groups which was characterised as a reduction in haemoglobin concentration, red blood cell count, and packed cell volume which was apparently associated in a dose-related manner with an increased methaemoglobin concentration and an observable increase in Heinz body formation. At 3,000 mg/kg there was a slight reticulocytosis noted in both sexes. This was accompanied in females by a shift in the differential leucocyte count noted as an increase in the percentage of polymorphonuclear neutrophils and a decrease in the percentage of lymphocytes. Small changes were observed at the highest dose level in alkaline phosphatase activity, which was slightly increased in male mice. At the same dose level, total protein concentration was slightly reduced in female mice. There were no abnormal results in the urinalyses.

In the animals that died or were sacrificed within the first two week period, all were found to be emaciated and in poor general condition. In all treated animals dying during the test period, congestion of the organs, especially of the liver, was observed. At the highest concentrations, atrophy of thymic tissue was observed. There was an increased haemosiderosis at the two highest dose levels. There were no other pathological findings associated with the occurrence of chlordimeform in the diet (Sachsse, 1979b).

Groups of mice (30 males and 30 females/group), housed under SPF conditions, were fed N-formyl-4-chloro-o-toluidine in the diet at dosage levels of 0, 750, 1,500, 3,000 or 6,000 mg/kg for 60 days. These dosage levels corresponded to dietary intakes of 0, 138, 379, 1,203, or 3,153 mg/kg bw/day for females and 0, 140, 349, 1,023, 2,549 mg/kg bw/day for males. All animals were subjected to a complete haematological, clinical chemistry, and urinalysis examination at the end of the 60-day experimental period. Groups of 10 males and 10 females from each group were examined for gross and microscopic
pathological changes at the conclusion of the study.

Mortality was observed predominantly at the high dose level over the course of the study. There were no clinical signs of poisoning although food consumption and growth were depressed. Growth was significantly depressed at 1,500 mg/kg and above in both males and females over the course of the study. Ophthalmologic and auditory examinations showed no effect of the presence of the chlordimeform metabolite in the diet.

Significant haematological abnormalities were observed at all dose levels at the conclusion of the study. Toxic haemolytic anemia in both males and females was characterised as a reduction in haemoglobin concentration, erythrocyte count, packed cell volume and methaemoglobinemia accompanied by an increased number of Heinz bodies. Additionally, both males and females in all treated groups showed a significant reticulocytosis, thrombocythemia, and leucocytosis. At higher concentrations in both males and females, the leucocytosis was accompanied by a shift in the differential leucocyte count.

Slight changes were noted with respect to several blood chemistry parameters reflective of hepatic function (an increased activity of SCOT, SGPT, and SAP). Urinalysis revealed a somewhat lower specific gravity and the presence of bile pigment in animals treated with the two highest dietary concentrations.

Microscopic examination of tissues and organs revealed cytomegaly and hyperplasia of the bile duct epithelium and kupffer cells in some animals at 750 mg/kg and in most animals at the higher dose levels. Nuclear inclusion bodies were also evident in all treated animals and at the highest dose level, moderate centrolobular fatty changes were observed. Additionally at the high level, atrophy of thymic lymphoid tissue and of splenic white pulp was observed. Substantial hyperplasia of the epithelium of the urinary bladder was observed in most animals at the highest dose level and sporadically throughout the treated groups. (This hyperplasia was associated with apoptosis, a form of cell death characterised by condensation and fragmentation of the cell into discrete membrane-bound bodies which are either shed from epithelial surfaces or ingested by other cells and degraded) (Sachsse et al., 1980b).

Long-term studies

[In three basically identical studies, chlordimeform and its two principal metabolites, N-formyl-4-chloro-o-toluidine and 4-chloro-o-toluidine, were tested in rats using a standard protocol to define carcinogenic hazards from long-term, dietary administration. Preliminary results of these studies were previously reported and the following is a complete evaluation of the final reports.]

Rats

Groups of rats (90 males and 90 females/group), Tif:RAIf strain, maintained under SPF conditions were fed chlordimeform in the diet for 24 months at dosage levels of 0, 2, 20, 100 or 500 mg/kg. These
dietary levels based upon food consumption data were equivalent to
dosage levels of 0, 0.1, 1.0, 5.0 and 24 mg/kg bw/day for males and 0,
0.1, 1.2, 6.0, and 28 mg/kg bw/day for females. At the conclusion of
the dietary feeding study, all remaining rats were fed control diets
for a period of time until a survival rate of 20% per sex (10 rats)
per group was attained, at which time the animals were sacrificed and
examined.

Groups of 20 male and 20 female rats per group were examined
periodically (4, 13, 26, 52, 78 and 104 weeks) for clinical laboratory
investigations including haematology, blood chemistry and urinalyses.

Groups of 10 animals/sex/group were sacrificed at 27 and 52 weeks for
gross and microscopic examinations of tissues and organs. Note: it
appears that at 106 weeks, all the remaining animals were killed and
examined for gross changes (organ weight and ratio data) and tumour
pathology. A complete terminal microscopic pathology was performed on
10 rats sacrificed at the end of the experiment. Additionally all
rats dying between 12-24 months are reported. There is no specific
106-week microscopic pathology and while the report is not usual in
some respects it is very complete and totally acceptable. At the
conclusion of the study, all animals sacrificed (also those that died
prior to the termination) were examined for gross and microscopic
pathology.

Excessive mortality was not observed over the course of the study.
Growth and body weight were maintained in all groups with the
exception of the 500 mg/kg level where growth in both sexes was
slightly retarded. There were no clinical signs of poisoning or
abnormal behaviour. Survival with respect to the extended duration of
the study (beyond 24 months) was not affected by chlordimeform.
Sacrifice of each group of rats was made when mortality reached 20%
(10 rats surviving). Each sacrifice date was unrelated to the dietary
dosage, indicating that chlordimeform did not affect the longevity of
the exposed rats. Pathology examination made at the conclusion of the
study (either 24 months for gross or terminal for microscopic) did not
indicate adverse effects of chlordimeform exposure. Ophthalmologic
and auditory examinations, performed at periodic intervals, revealed
no adverse effects attributable to chlordimeform. Methaemoglobinaemia
was observed at dose levels of 20 mg/kg and above. At week 4, both
males and females showed a slight, but statistically significant,
increase in methaemoglobin content. At weeks 13 and 26, this
condition abated but returned at the end of one year and was
significant in both sexes at the highest dose group for the remainder
of the study. Changes in several other blood chemistry parameters
were observed at the highest dose level. Heinz body formation
generally associated with methaemoglobinaemia was not observed at week
4 but at the end of one year and thereafter, Heinz bodies were
observed at the highest dose level. A slight but significant
reduction in blood glucose concentration was noted at the highest dose
level throughout the majority of the study. Slight changes in the
urinalysis were observed in the highest dose group. This was
manifested as a slightly reduced urinary volume and a slightly higher
specific gravity observed in the youngest animals. Ketonuria and
proteinuria were observed in the youngest animals fed 500 mg/kg. This
was noted only at the earliest examination periods and urinalysis
performed at 13 weeks and thereafter for the remainder of the study did not reveal these occurrences.

Gross pathology and organ weight data (provided for 27, 52 and 106-week sacrifice intervals) did not show any significant dose-related responses. While several organ weight and organ to body weight or brain weight ratios showed statistically significant differences from control animals, the findings were not dose related and the biological significance of these random occurrences is doubtful. Microscopic histopathologic analyses of tissues and organs (performed at weeks 27 and 52 and at the termination of the study) indicated no significant changes attributable to chlordimeform in the diet. Although numerous benign and malignant tumours were observed in both treated and control animals, the frequency and type of neoplasms, reported at 12 and 24 months with pathology analyses, were not dose-related nor were they attributable to chlordimeform. Several congenital, degenerative, or inflammatory changes were attributed to disease, common in older animals.

Based on the haematologic occurrence of methaemoglobinaemia in young rats, the no-effect level of chlordimeform for rats is 2 mg/kg in the diet, corresponding to an intake of 0.1 mg/kg bw/day. Over the course of the study, there was no indication of carcinogenic potential to rats as a result of the presence of chlordimeform in the diet (Sachsse et al., 1980c).

Groups of rats (90 males and 90 females/group), housed under SPF conditions, were fed N-formyl-4chloro-o-toluidine in the diet at dosage levels of 0, 2, 20, 100, or 500 mg/kg for two years. These dosage levels were estimated to correspond to dietary intakes of 0, 0.1, 1.0, 5 or 30 mg/kg/day for females and 0, 0.1, 1.0, 4.0 or 24 mg/kg for males. Groups of 10 males and 10 females were sacrificed at periodic intervals (26 and 52 weeks) for gross and microscopic pathology examinations. Complete haematological, clinical chemistry, and urinalysis examinations were performed at 4, 13, 26, 52 and 78 weeks on 20 males and 20 females of each group. At 24 months, 20 males and 20 females were sacrificed and examined for clinical laboratory parameters and gross pathology. The remaining animals were fed control diets for additional periods of time until a survival rate of 20% per sex per group was attained. At that time the remaining animals were sacrificed and examined microscopically for pathological changes. All animals were examined for pathological events, especially neoplastic and non-neoplastic lesions.

In the high dose group food intake and growth were affected over the course of the study and slight growth retardation was observed. Clinical signs of toxicity or adverse behaviour were not observed. There was no mortality in the study attributable to the presence of N-formyl-4-chloro-o-toluidine. Sacrifice of each group of males and females was made when mortality reached 20%, and each sacrifice date was not related to dietary dosage. This chemical did not affect the longevity of the exposed animals. Tissue pathology did not show adverse effects of dietary treatment. During the course of the study, no adverse clinical signs of poisoning were observed. Ophthalmologic examinations and auditory tests were normal. The results of the haematological investigation showed haemoglobin concentration to be
slightly, but significantly, below that of the controls in both male and female rats at the two highest dosage levels. In addition, slight but significant decreases in the erythrocyte count and packed cell volume, a slight increase in reticulocytes and somewhat higher methaemoglobin values were also seen in both male and female rats at 500 mg/kg.

With the exception of lower body weights of the animals at the highest concentration, the most obvious change was a significant increase in absolute and relative liver weights seen in both sexes, but more pronounced in females, in the 500 mg/kg group.

A significantly increased incidence of hyperplasia of small biliary ducts was seen in the liver of rats of the 500 mg/kg concentration group. In rats of the 500 mg/kg group, which were sacrificed after 2 years or died after 12 months, a marked increase in frequency of multiloculated cholangiogenic biliary cysts in the liver was noted. Both of these findings were more pronounced and more frequent in female that in male animals. The incidence of biliary lesions in rats fed dietary concentrations of 100 mg/kg or below was not significantly higher than that noted in the controls.

Numerous benign and malignant tumours were observed in both control and treated rats. The frequency and types of neoplasms occurring in these animals were not influenced by the N-formyl metabolite in the diet. All gross and histopathological lesions and changes seen in both control and test animals were described as congenital, degenerative, or inflammatory in origin and were attributed to naturally occurring diseases common in aged rats. There was no oncogenic potential in this species with N-formyl-4-chloro-o-toluidine, the chlordimeform metabolite. A no-effect level in this study is 20 mg/kg in the diet (Sachsse et al., 1980e).

Groups of rats (90 males and 90 females/group), housed under SPF conditions, were fed 4-chloro-o-toluidine in the diet at dosage levels of 0, 2, 20, 100 or 500 mg/kg for two years. These dosage levels corresponded to dietary intakes of 0, 0.1, 1.0, 5, or 28 mg/kg/day for females and 0, 0.1, 1.0, 4.6 or 24.6 mg/kg/day for males. Groups of 10 males and 10 females were sacrificed at periodic intervals (27 and 54 weeks) for gross and microscopic pathology examinations. Complete haematological, clinical chemistry and urinalysis examinations were performed at 4, 13, 26, 52 and 78 weeks on 20 females and 20 males of each group. At 24 months, 20 males and 20 females were sacrificed and examined for clinical laboratory parameters. Several animals were examined for gross pathology. The remaining animals were fed control diets for additional periods of time until a survival rate of 20% per group was attained. At that time, the remaining animals were sacrificed and examined for microscopic pathology and oncogenic response. A complete microscopic analysis was made on at least 10 rats of each sex of each group at the termination of the experiment. All rats dying during the course of one study were examined for tumours or neoplasms.

In the high dose group of females food intake and growth were affected over the course of the study and slight growth retardation was
observed. There was no effect on male growth at any dose level. Clinical signs of toxicity or adverse behaviour were not observed. There was no mortality in the study attributable to the presence of the chlordimeform metabolite. As noted with chlordimeform and the N-formyl metabolite, the extended duration of the study beyond the 24-month-sacrifice date was not affected by 4-chloro-o-toluidine in the diet. Sacrifice of each group of males and females, made when mortality reached 20%, was made at random dates not reflective of a dietary dose-response. Again, this metabolite did not affect longevity of the exposed animals and tissue pathology was uneventful. Ophthalmologic examinations and auditory tests did not reveal changes that were related to the administration of 4-chloro-o-toluidine.

The results of the haematological investigation, blood chemistry data, and the urine analysis were similar for both treated and control rats. Periodically, the haemoglobin concentration was slightly but significantly below that of the controls in the female rats at 100 mg/kg and above. Slight, but significant decreases were observed in the erythrocyte count and packed cell volume in the female rats at 500 mg/kg. Marginal reticulocytosis was also found to occur at 500 mg/kg in the female rats at week 13 and in both sexes at week 26. In both male and female rats at 500 mg/kg, the methaemoglobin level was found to be slightly, though significantly, increased when compared to controls. Periodically, this change was observed in the females of the 100 mg/kg dosage group and, occasionally, Heinz bodies were also observed in female rats.

Organ weights, organ to body weight ratios, and organ to brain weight ratios revealed some statistically significant differences between treated and control animals. With the exception of the absolute and relative liver weights at the conclusion of the study, these findings were not dose-related.

In rats from the 500 mg/kg dosage group, a slightly but significantly increased incidence of multilocular cholangiogenic cysts was observed in the liver. These biliary cysts were seen in 10/89 female and in 3/90 male rats from the 500 mg/kg group, but only in 4/89 female and in none of the male control animals (9/90). The incidence of cholangiogenic cysts in rats at the lower dosage groups was similar to that in the controls.

Numerous benign and malignant tumours were observed in both control and treated rats. The frequency and types of the neoplasms occurring in these animals were not influenced by the presence of 4-chloro-o-toluidine in the diet. Gross and histopathological lesions and changes seen in both control and test animals were described as congenital, degenerative, or inflammatory in origin and were attributed to naturally occurring diseases, common in aged rats. Based on these data, there was no evidence of carcinogenic potential. A no-effect level in this study is 20% mg/kg in the diet (Sachse et al., 1980d).

OBSERVATIONS IN MAN

The 1979 Meeting (FAO, 1980) requested that future Meetings be informed of results of occupational exposure surveillance programs.
Such data have been made available in summary form concerning the agricultural situation with chlordimeform in nine countries. Surveys of aerial pesticide applications to cotton entailed the monitoring of about 600 airstrips in 1979 in the nine countries. Over 28,000 urine samples were analysed from workers in all phases of the application situation. The urine was monitored and residue data expressed as chlordimeform equivalents.

Only 1% of the assays showed substantial chlordimeform urinary residues indicating a significant occupational exposure. Over 75% of the samples were at or below the lowest level of the analytical capability. In general, the conditions in two countries, the USA and Australia, were indicative of a favourable working relationship where only about 1% of the samples contained a residue level indicating a higher than desired level of exposure. Working conditions in some of the other countries (i.e., Colombia, El Salvador, Guatemala, and Honduras) were less favourable. There was an improvement made in these areas but, because of limitations in acceptable equipment and educated people, the exposure picture was less than optimal. However, in some areas where flagmen were (had to be) intentionally exposed, the urinary residue samples were low, indicating that with precautions exposure can be limited. In all cases, even with the highest exposure of individuals, there were no cases of haematuria. The monitoring of exposure and education of agricultural operators in the appropriate use of chlordimeform to minimize exposure in continuing (Kossmann, 1980).

EVALUATION

COMMENTS

Chlordimeform, an insecticide and acaricide, was reviewed in 1971, 1975, 1978, and 1979 (FAO/WHO, 1972b, 1976b, 1979b, 1980b). In 1978, it was reported that chlordimeform and its principal metabolites were carcinogenic in the mouse, producing a dose-related malignancy, histologically characterized as haemangioendothelioma.

Carcinogenicity studies with rats produced conflicting results and were repeated. Several short-term bioassay systems had demonstrated mutagenicity with the chlordimeform metabolite 4-chloro-o-toluidine. In 1979, two studies confirmed the carcinogenicity of 4-chloro-o-toluidine in mice and the lack of it in rats.

Information requested by previous meetings was reviewed. Extensive long-term carcinogenicity studies in rats with chlordimeform and its two major metabolites confirmed the lack of a carcinogenic response in this species. Based on toxicological and clinical data, no-effect dietary levels were estimated for chlordimeform and its metabolites in the rat and dog.

Monitoring agricultural workers has showed that whilst minimal exposure can occur in controlled situations under less well controlled conditions, occupational exposure can be a significant problem and control of exposure is recommended.

No further data have been submitted on the incidence of a haemorrhagic
cystitis. This occurrence has not been reported again.

In consideration of all of the available data on metabolism, teratogenicity, mutagenicity, carcinogenicity and toxicity as well as the current uses of chlordimeform in agriculture, the meeting re-affirmed the temporary ADI and required a review of the epidemiology programme.

Level causing no toxicological effect

Rat: 2 mg/kg in the diet equivalent to 0.1 mg/kg bw/day.
Dog: 250 mg/kg in the diet equivalent to 6.25 mg/kg bw/day.

Estimate of temporary acceptable daily intake for man

0-0.0001 mg/kg bw/day.

FURTHER WORK OR INFORMATION

Required (by 1985)

Report on continued surveillance and epidemiological studies of occupationally exposed workers in both industry and agriculture.

Desirable

Confirmatory long-term animal bioassay using a third species for evaluation of the potential carcinogenic hazard.

REFERENCES


Sachsse, K., Suter, P., Leutkemeier, H., Zak, F. and Hose, R. Chlordimeform-HCl - Lifespan (Chronic Toxicity and Carcinogenicity)


See Also:
- Toxicological Abbreviations
  - Chlordimeform (EHC 199, 1998)
  - Chlordimeform (ICSC)
  - Chlordimeform (WHO Pesticide Residues Series 1)
  - Chlordimeform (WHO Pesticide Residues Series 5)
  - Chlordimeform (Pesticide residues in food: 1978 evaluations)
  - Chlordimeform (Pesticide residues in food: 1979 evaluations)
  - Chlordimeform (Pesticide residues in food: 1985 evaluations Part II Toxicology)
  - Chlordimeform (Pesticide residues in food: 1987 evaluations Part II Toxicology)
  - Chlordimeform (IARC Summary & Evaluation, Volume 30, 1983)