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Aldicarb

Guideline

The maximum acceptable concentration (MAC) for aldicarb in drinking water is 0.009 mg/L (9 µg/L). This guideline is considered to be applicable to the total of aldicarb plus its toxic metabolites, aldicarb sulphoxide and aldicarb sulphone.

Identity, Use and Sources in the Environment

Aldicarb is the common name for 2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)-oxime, which is represented by the empirical formula $C_7H_{14}N_2O_2S$.

The vapour pressure of aldicarb is 13 mPa at 20°C. Its solubility in water is 6 g/L at 25°C, and it is stable in neutral, acidic and weakly alkaline media. Aldicarb is oxidized relatively quickly to aldicarb sulphoxide and more slowly to aldicarb sulphone,[1] both of which are more soluble in water than the parent compound (330 and 10 g/L, respectively, at 25°C).[2] Reported log octanol–water partition coefficients for aldicarb range from 0.70 to 1.13.[3]

Aldicarb is a broad-spectrum, systemic carbamate insecticide used to control a variety of insects, mites and nematodes. Since its introduction in 1970, aldicarb has been registered for use on citrus crops, dry beans, grain, sorghum, ornamentals, pecans, peanuts, potatoes, seed alfalfa, soybeans, sugar beets, sugarcane, sweet potatoes and tobacco. Less than 25 000 kg were used in Canada in 1986.[4]

Aldicarb degrades in soil to essentially non-toxic concentrations with a half-life ranging from a few days to more than two months.[5,6] The primary mode of degradation to the sulphoxide and sulphone is oxidation by soil micro-organisms[7]; degradation to non-carbamate compounds appears to occur by microbial decay as well as by hydrolysis, depending on soil conditions.[6] Factors influencing the rate of degradation are moisture, organic matter and oxygen content of the soil, pH and temperature.[1,5,6,8–11]

Aldicarb and its degradation products are generally mobile in soil.[5,6] Leaching is most extensive in sandy or sandy loam soils,[5] as adsorption to soil is a function of the organic matter content.[12] As aldicarb, aldicarb sulphoxide and aldicarb sulphone have low reported partition coefficients in soils with low organic matter content (K_{oc} values range from 0 to 47), these compounds can potentially contaminate groundwater.[11]

Aldicarb is very persistent in groundwater. It degrades to non-toxic products with a half-life that ranges from a few weeks to as long as several years under typical conditions.[8] The primary mode of degradation is chemical hydrolysis, although there may also be some microbial decay in shallow groundwater.[13] Aldicarb sulphoxide and aldicarb sulphone residues are found in approximately a 1:1 ratio in groundwater.[5,6] Factors affecting the rate of disappearance in water are temperature and pH.[7,14]

Exposure

In a survey of 317 wells in eastern Canada in September 1986, aldicarb was detected in 167 of 782 samples; concentrations were above 10 ppb in only 9% of the 167 samples.[15] In surveys of private and municipal drinking water supplies in five Canadian provinces, conducted from 1980 to 1986, aldicarb was detected in 111 of 1017 samples (detection limits ranged from 0.01 to 3.0 µg/L); the maximum concentration was 28 µg/L.[16] In Prince Edward Island during 1985 and 1986, 77 of 96 samples (80%) in two areas contained aldicarb residues above the detection limit of 0.1 µg/L, with a maximum of 16.4 µg/L.[17] In the same province, groundwater quality was monitored between 1985 and 1988 near two potato fields to which aldicarb was applied at planting once or twice between 1983 and 1986. In May 1988, concentrations of aldicarb plus its degradation products exceeded 9 µg/L in 12% of 48 well samples.[18] Residues of aldicarb and its sulphoxide and sulphone have also been reported frequently in water samples in a number of U.S. states; concentrations are typically in the range 1–50 µg/L, and a maximum of

400 µg/L was recorded in one case from Long Island, New York.[19]

In analyses of 778 samples of various food commodities between 1982 and 1992, carried out by the Bureau of Field Operations, Health and Welfare Canada, detectable residues of aldicarb were found only in samples of potatoes from the 1984–85 crop year; aldicarb concentrations ranged up to 0.78 ppm in 28 of 74 samples of potatoes. No samples of any commodity contained aldicarb sulphone (n = 212) or aldicarb sulphoxide (n = 185).[20] In U.S. surveys, aldicarb sulphoxide was found in seven of 6391 samples of agricultural commodities between October 1, 1981, and September 30, 1986, at levels at or below 1.0 ppm.[21] In a 1982 U.S. survey of citrus fruits, aldicarb was not detected in oranges; however, the aldicarb concentration in one sample of grapefruit was 50 µg/kg. In other U.S. surveys, aldicarb was detected in 78% of potatoes sampled in 1979 at concentrations up to 470 µg/kg and in 94% of potatoes analysed in 1980 at concentrations ranging from 50 to 520 µg/kg.[22] In another survey of potatoes in the United States, conducted from 1980 to 1983, aldicarb and its degradation products were found in 48 of 81 samples, four of which contained levels above 0.5 ppm.[23] Based on its low octanol–water partition coefficient, aldicarb is not likely to bioaccumulate to a significant degree in animal tissue.[3]

The Canadian maximum residue limits established prior to 1991 for aldicarb in food allowed for the possibility of exposure that was close to the adverse effect level in young children and adolescents who consumed large quantities of fresh citrus fruit or cooked potatoes. The maximum residue limits were therefore lowered from 0.1 to 0.06 ppm for citrus juice and from 0.5 to 0.1 ppm for potatoes.[20] The latter precluded the use of aldicarb on potatoes, its major use in Canada, as the effective dose for mitigating insect infestation on potatoes is 0.5 ppm. In the United States, the average daily intake of aldicarb for a 25- to 30-year-old male has been estimated to be 0.0002 mg/kg bw, based on U.S. monitoring data for residues in foods.[24]

Analytical Methods and Treatment Technology

Aldicarb and its sulphoxide and sulphone oxidation products can be determined simultaneously by capillary gas chromatography. The sample is extracted with methylene chloride, evaporated at low temperature (<40°C) to prevent oxidation of aldicarb to the sulphone and injected at 200°C for detection as the respective nitriles with a nitrogen–phosphorus detector. The detection limit is 1 µg/L for all three compounds.[25]

Aldicarb and its metabolites were formerly quantifed as total aldicarb by conversion of aldicarb and aldicarb sulphoxide to the sulphone by hydrogen peroxide – acetic acid oxidation and separation by gas–liquid chromatography, followed by flame photometric detection.[26,27] This method is not suitable for quantification of the individual species, and it is tedious and subject to error.[11]

High-performance liquid chromatography (HPLC) is often the method of choice and is the basis of U.S. EPA Method 531 for carbamate pesticides.[28] Aldicarb, its sulphoxide and its sulphone are separated by reversed-phase HPLC, and the analytes are then hydrolysed to methylamine followed by post-column derivatization with ortho-phthalaldehyde and fluorescence detection. The detection limits are 1.3, 0.8 and 0.5 µg/L for aldicarb, the sulphoxide and the sulphone, respectively.[11,29]

As aldicarb is rapidly degraded to the sulphone and sulphoxide metabolites in the environment, appropriate treatment technology must be able to remove all three compounds efficiently. Granular activated carbon adsorption in home treatment devices has been found to be approximately 99% effective in removing a 200 or 1000 ppb mixture of aldicarb, aldicarb sulphoxide and aldicarb sulphone in a ratio of 10:45:45.[19] Chlorination has been investigated as a potential means of removing aldicarb from drinking water, as all residues are converted to aldicarb sulphoxide within minutes. The normal degradation of the sulphoxide to the sulphone is not affected. Both the sulphoxide and the sulphone are then degraded into unidentified products. Depending upon the toxicity of these unidentified degradation products, this method may prove to be feasible.[19] Aeration, or air stripping, has not been found to be very efficient in the removal of aldicarb from drinking water.[30]

Health Effects

Pharmacokinetics and Metabolism

Aldicarb is rapidly absorbed from the gastrointestinal tract, the respiratory tract and the skin. The metabolic pathway for aldicarb is similar in all species studied. Aldicarb is rapidly oxidized to aldicarb sulphoxide, which is further metabolized more slowly by oxidation and hydrolysis to aldicarb sulphone. Both metabolites as well as the parent compound are degraded to the corresponding oximes and nitriles, which are broken down into aldehydes, acids and alcohols. Ingested aldicarb sulphoxide and aldicarb sulphone are metabolized in the same manner as the parent compound.[1,31]

Elimination of aldicarb is rapid; it does not accumulate in tissues. In rats, 80% of an orally administered dose of radioactively labelled aldicarb was eliminated in the urine within 24 hours; 4% was detected in the faeces; none was detected in tissues by

the fifth day.[32] Enterohepatic circulation of metabolites following oral exposure has been reported. In bile duct cannulated rats administered a single dose of 0.1 mg/kg bw aldicarb ^{14}C-thiomethyl in vegetable oil by intubation, 28.6% of the dose was eliminated in the bile within 48 hours.[33] Aldicarb appears to cross the placental barrier, based on the toxic effects observed in foetuses of rats administered aldicarb by gastric intubation.[34,35]

Aldicarb inhibits the action of acetylcholinesterase at neural synapses of both the central and peripheral nervous systems by reversible complexation. Without removal by the enzyme, acetylcholine accumulates at the receptor sites of the junction, resulting in the inability of the target muscle or nerve to return to its resting state. The aldicarb–acetylcholinesterase complex may dissociate to form aldicarb and the enzyme, or it may decompose into a carbamylated enzyme plus the oxime. The carbamylated enzyme is then hydrolysed into the free enzyme and methyl carbamic acid, thus detoxifying the insecticide.[31,36]

Human Health Effects

Clinical symptoms of aldicarb intoxication are cholinergic in nature and include dizziness, weakness, diarrhoea, nausea, vomiting, abdominal pain, excessive perspiration, blurred vision, headache, muscular fasciculations or convulsions, temporary paralysis of the extremities and dyspnoea. Recovery is rapid, usually within six hours.[36] Aldicarb is considered to be one of the most acutely toxic pesticides,[37] with several incidents of accidental or intentional poisoning being reported.[1,38,39] Poisoning has resulted from ingestion of produce such as melons and cucumbers containing low levels of aldicarb and aldicarb metabolites.[40–43] In one report of illness resulting from ingestion of contaminated cucumbers, the dose was estimated to be in the range 0.006–0.25 mg/kg bw.[40] In incidents involving contaminated melons, estimates of the dose of aldicarb that caused illness were as low as 0.0021 mg/kg bw.[44]

In a human volunteer study, groups of four adult males ingested aqueous aldicarb in single doses of 0.025, 0.05 or 0.10 mg/kg bw. Whole blood acetylcholinesterase activity was measured at 18 hours and one hour prior to exposure and at one, two, four and six hours following exposure. Cholinergic symptoms were observed in the highest dose group. A dose-related depression of acetylcholinesterase activity, predominantly in the first two hours following exposure, was observed in all subjects. Based on the highest pre-exposure acetylcholinesterase levels, the mean values for maximum percent inhibition in the 0.025, 0.05 and 0.10 mg/kg bw dose groups were 47, 64 and 73%, respectively. It should be noted, however, that acetylcholinesterase levels in individuals varied considerably between 18 hours and one hour pre-dosing (e.g., 167 versus 85 µmol/mL per hour in one subject), and the author commented that the radiometric method of analysis employed may not reflect true acetylcholinesterase levels in the red blood cells. All of the volunteers reported feeling normal after six hours.[45] In a similar study, two volunteers ingested doses of aqueous aldicarb of 0.05 or 0.26 mg/kg bw. Clinical signs of intoxication were observed only in the subject receiving 0.26 mg/kg bw.[46]

In a double-blind, placebo-controlled human volunteer study carried out in 1992 for Rhone-Poulenc,[47] single oral doses of aldicarb were administered in orange juice to 39 males (0, 0.01, 0.025, 0.05 and 0.075 mg/kg bw; one male received 0.06 mg/kg bw by accident) and nine females (0, 0.025 and 0.05 mg/kg bw) (six men and five women received both a dose and a placebo at different times). An inhibition of 20% or greater in red blood cell cholinesterase was observed at 0.025 mg/kg bw in one of eight males and two of four females, and reductions were statistically significant in that and higher dose groups. One male at 0.06 mg/kg bw demonstrated profuse whole body sweating, considered an aldicarb-related cholinergic symptom; one male at each of 0.05 and 0.025 mg/kg bw also showed slight localized sweating, thus possibly giving some indication of a dose–response relationship. In females, the only clinical sign was a slight increase in saliva at 0.05 mg/kg bw. Inhibition of plasma cholinesterase occurred at all doses but was not considered to be adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 0.01 mg/kg bw for erythrocyte cholinesterase inhibition and sweating, a clinical symptom.[48]

The effects of chronic ingestion of aldicarb on human immune function were investigated in a limited cross-sectional epidemiological study of 50 women between the ages of 18 and 70 in Wisconsin. Twenty-three of the women ingested drinking water containing detectable levels of aldicarb (range 1–61 ppb, mean 16.1 ppb) daily; the other 27 women consumed water containing no detectable aldicarb (<1 ppb). Data on length of residency or duration of exposure were not reported. Based on information on health status obtained by interview, recorded fluid intake and the results of laboratory immune function blood tests, the authors concluded that there was an association between consumption of aldicarb-contaminated drinking water and abnormalities in various subsets of T-cell populations in women with otherwise intact immune systems. Women in the exposed group had increased numbers of T8 cells, an increased percentage of total lymphocytes as T8 cells and a decreased ratio of T4:T8 cells. Response to the antigen *Candida* in a lymphocyte

stimulation assay was also elevated in exposed women. These findings were significantly correlated with daily aldicarb ingestion in drinking water. No clinical evidence of immunodeficiency was reported in any of the women.[49]

This study has been reviewed by government agencies in Canada and the United States,[48] as well as by independent panels of experts.[50] The limitations of the study noted by these reviewers include the small size of the exposed group, the failure to calculate aldicarb dose on a body weight basis (which prevented construction of a meaningful dose–response relationship), the failure to match exposed and control groups with respect to water supply (the exposed group was served by private wells, whereas half of the control group was supplied by municipal sources) and the failure to determine the presence of other possible contaminants in the drinking water. Moreover, although there was a significant difference in the values for T8 cell counts and the ratio of T4:T8 cells between the exposed and the control groups, both were within the normal range.[31] The consensus of the reviewers was that the study provides little evidence for immunotoxic effects caused by aldicarb exposure.

One of the criticisms mentioned above, namely the failure to determine the presence of other contaminants in the drinking water supply, was addressed in a follow-up in 1987 of 45 of the 50 women in the original Wisconsin study. Only five individuals were found to be currently exposed to aldicarb (mean daily intake of aldicarb estimated to be 0.022 µg/kg bw). The protocol of the follow-up was similar to that of the original study, but drinking water was analysed for a number of additional organic and inorganic parameters. No adverse clinical effects were reported; however, in the five exposed women, the mean percentage of lymphocytes (50% versus 36% in the 40 unexposed women drinking water from private or municipal supplies), the mean number of CD2+ T cells (formerly referred to as T11 cells; 2606 versus 1850 cells/mm^3) and the mean number of total CD8+ T cells (formerly T8 cells; 1069 versus 563 cells/mm^3) were increased. However, the difference in the mean percentage of lymphocytes was significant only when the exposed women were compared with unexposed women drinking municipal tap water. Unlike the previous study, no differences in the *Candida* stimulation assays or the ratio of CD4+ (formerly T4 cells) to CD8+ T cells were noted. Three of the individuals exposed to detectable aldicarb concentrations in the earlier study had installed activated carbon filters in their homes. The mean absolute CD8+ T cell count for these individuals had decreased by almost 50% since 1985, and the percentage of CD8+ T cells had decreased from 30% to 20%. There was a 23% increase in the absolute CD8+ T cell count in one woman who was unexposed in 1985 but was now exposed to aldicarb in her drinking water, although there was no significant change in the percentage of these cells. There were no significant associations with any of the other drinking water contaminants measured. The authors concluded that, in spite of the extremely low power of this study to detect differences, changes in the cellular distribution of immune system parameters were observed in women exposed to aldicarb in their drinking water.[51] However, this follow-up adds little weight to the results of the original study, as it has many of the same limitations. Further research on the effects of aldicarb on the immune system is, however, warranted.

In a pilot study in Suffolk County, New York, the relationship between levels of aldicarb in drinking water and delayed neuropathy was investigated. Information on rather subjective symptoms was obtained from 641 individuals by self-administered questionnaire; no clinical examinations were conducted. The overall response rate was poor (19.9%). Based on the number of positive responses on the questionnaire, the results for each individual were classified as being vaguely, possibly or probably suggestive of a neurological syndrome. Respondents were divided into four exposure groups based on aldicarb concentrations in their drinking water: 8–15 ppb, 16–35 ppb, 36–66 ppb and >66 ppb. There was a significant association between the age-adjusted rates for all neurological syndromes (i.e., combined vague, possible and probable) and increasing aldicarb concentration. It was not reported whether the subjects were classified blindly on the basis of the results of the questionnaire or whether the respondents were aware of their exposure status. The authors recommended further studies to investigate this association.[52]

In 1035 residents of 462 households in Long Island, New York, information on food consumption, symptoms experienced and illnesses diagnosed was obtained by self-administered questionnaire. There was a possible association between aldicarb exposure and diarrhoea; however, this association was not confirmed in a similar follow-up study involving children. There was no relationship between aldicarb concentrations in drinking water or food and other reported symptoms or diagnosed illnesses.[53]

Health Effects in Experimental Animals and *In Vitro*

Acute and Short-Term Toxicity

Aldicarb is highly acutely toxic in animals; the oral LD_{50} in rats ranges from 650 to 930 µg/kg bw,[54] depending on the vehicle. Aldicarb is most acutely toxic when administered in corn or peanut oil.[36] The oral LD_{50} in rats for aldicarb sulphoxide is similar to

that of the parent compound, whereas the LD_{50} for the sulphone is approximately 25 times higher.[31]

A mixture of 1:1 aldicarb sulphoxide:aldicarb sulphone (the ratio of concentrations generally present in drinking water) was administered in drinking water to Wistar rats (10 per sex per group) at nominal concentrations of 0, 0.075, 0.3, 1.2, 4.8 or 19.2 ppm for 29 days. Plasma and erythrocyte cholinesterase activities were measured at eight, 15 and 29 days of treatment, and brain cholinesterase activity was determined at terminal sacrifice (29 days). Body weight gain was reduced in both sexes in the highest dose group, as was water consumption; food consumption was reduced only in males in this group. Mean plasma cholinesterase activity was reduced in both males and females in the highest dose group for all three sampling periods (68, 77 and 73% reduction in males and 74, 74 and 65% reduction in females, respectively). Mean erythrocyte cholinesterase activity was also depressed in both sexes exposed to 19.2 ppm (57, 63 and 59% in males and 54, 58 and 63% in females for the three sampling periods). In male rats exposed to 4.8 ppm, there was a 28% reduction in plasma cholinesterase activity at day 8 of exposure and a 25% reduction in erythrocyte cholinesterase activity at day 29. Brain cholinesterase activity was reduced 10% in females in the highest dose group at the end of the study. There was no aldicarb-related mortality or clinical signs of acetylcholinesterase inhibition. The researchers considered the effects observed in males exposed to 4.8 ppm to be of questionable biological significance and considered the "no-ill-effect level" to be 4.8 ppm, which they stated was equivalent to a dose of 0.5 mg/kg bw per day. Based on analysis of the drinking water administered to the rats, the actual concentration averaged approximately 80% of the nominal concentration.[55] Therefore, the NOAEL would be 0.4 mg/kg bw per day.

The effects of aldicarb and aldicarb metabolites administered in the diet have been investigated in several early short-term studies in rats, mice and dogs,[56–66] reviewed by the FAO/WHO.[1] In several of these studies, cholinesterase activity was not determined or was measured one or two days following cessation of treatment. In view of the rapidly reversible nature of the inhibition of cholinesterase activity induced by aldicarb, these studies do not provide adequate information to determine NOAELs.

In two recent monkey studies, two groups of cynomolgus monkeys were given a single feeding of bananas prepared to provide 0 or 0.005 mg/kg bw per day of aldicarb sulphoxide/aldicarb sulphone residues. No deaths or clinical signs were reported. Plasma cholinesterase was depressed more than 20% at one, two and four hours and slightly depressed (13–14%) at six hours. No depression was seen at 12 or 24 hours. Maximum depression was noted at two hours. No effect on erythrocyte cholinesterase was apparent. The second study used the same design but used watermelon as the vehicle. Similar results were obtained, but peak plasma cholinesterase depression was observed at one hour.[67]

Subchronic and Chronic Toxicity

Groups of 10 rats per sex per dose level were fed dietary concentrations of aldicarb resulting in 0, 0.02, 0.1 or 0.5 mg/kg bw per day for 90–93 days. One male per group was sacrificed on days 1, 4 and 29 and one female per group was sacrificed on days 2 and 30 for cholinesterase determinations. Mortality was increased and body weight gain was depressed at 0.5 mg/kg bw per day. Although brain and erythrocyte cholinesterase activities were not affected, plasma cholinesterase was marginally depressed at 0.5 mg/kg bw per day. The no-observed-effect level (NOEL) was set at 0.02 mg/kg bw per day, based on the significantly increased mortality at the 0.5 mg/kg bw per day feeding level and a slight but non-statistically significant increase in mortality in the group fed at 0.1 mg/kg bw per day.[67]

Groups of rats (15 per sex per dose, strain unspecified) were fed diets containing concentrations of aldicarb sulphoxide equivalent to doses of 0, 0.125, 0.25, 0.50 or 1.0 mg/kg bw per day for six months, with an interim kill at three months. Growth was reduced in males at 0.25 mg/kg bw per day and above and in females at 1.0 mg/kg bw per day. Plasma and erythrocyte cholinesterase activities were depressed in males consuming 0.25 mg/kg bw per day and above and in females in the two highest dose groups. Additional groups of rats (five of each sex) were fed aldicarb sulphoxide in the diet equivalent to doses of 0, 0.0625, 0.125, 0.25, 0.50 or 1.0 mg/kg bw per day for three or six months. Some of the animals were sacrificed immediately following exposure, whereas others were placed on a control diet for 24 hours. Depressions in cholinesterase activity in animals sacrificed immediately after exposure were similar to those seen in the first part of the study. There was no cholinesterase inhibition in animals allowed to recover for one day before sacrifice. The NOAEL for cholinesterase inhibition was considered to be 0.125 mg/kg bw per day.[56]

In a two-year study, Carworth Farms-Elias rats (20 per sex per dose) were fed aldicarb in the diet at concentrations equivalent to 0, 0.005, 0.025, 0.05 or 0.1 mg/kg bw per day. Groups of 16 male and 16 female rats were also fed the same diets concurrently for one year and sacrificed at six and 12 months. There were no significant differences in any of the treated groups based on food consumption, mortality and life span, incidence of infection, relative liver and kidney weights, body weight gain, maximum body weight, haematocrit,

incidence of neoplasms, incidence of pathological lesions and brain, plasma and erythrocyte cholinesterase levels. Although the NOEL was assessed to be 0.1 mg/kg bw per day,[68] this study was not considered appropriate because of the small number of animals used and the absence of descriptions of the methods used for the measurement of cholinesterase inhibition.

In an additional two-year study, Greenacres Laboratory Controlled Flora rats (20 per sex per dose) were fed diets containing aldicarb (0.3 mg/kg bw per day), aldicarb sulphoxide (0.3 or 0.6 mg/kg bw per day), aldicarb sulphone (0.6 or 2.4 mg/kg bw per day) or a 1:1 mixture of aldicarb sulphoxide and aldicarb sulphone (0.6 or 1.2 mg/kg bw per day). Plasma cholinesterase activity and body weight gain were depressed in males consuming 1.2 mg/kg bw per day of the aldicarb sulphoxide/aldicarb sulphone mixture. Mortality was increased in male and female rats consuming 0.6 mg/kg bw per day of aldicarb sulphoxide. The authors considered the NOAELs to be 0.3 mg/kg bw per day for aldicarb and aldicarb sulphoxide, 2.4 mg/kg bw per day for aldicarb sulphone and 0.6 mg/kg bw per day for the 1:1 mixture of aldicarb sulphoxide and aldicarb sulphone.[69]

Weil and Carpenter[70] administered aldicarb in the diet to beagle dogs (three per sex per dose) at levels equivalent to 0, 0.03, 0.059 or 0.1 mg/kg bw per day for two years. No adverse effects on body weight, appetite, mortality, histopathology, haematology, biochemistry or terminal liver and kidney weights were observed in any of the dose groups.

Groups of beagle dogs (three per sex per dose level) were fed aldicarb at dietary concentrations of 0, 0.02, 0.04 or 0.075 mg/kg bw per day (0, 0.8, 1.6 or 3 ppm) for two years, five times weekly. No adverse effects on survival, body weight, food intake, absolute or relative liver or kidney weights, haematology, clinical chemistry, erythrocyte or brain cholinesterase activity or pathology were observed at any dose level. The NOEL was assessed at 0.075 mg/kg bw per day (3 ppm).[67]

A recent dog study exposed five groups of beagles to 95.5% pure aldicarb in the diet at doses of 0, 0.025, 0.05, 0.125 and 0.25 mg/kg bw per day (0, 1, 2, 5 or 10 ppm) for 12 months. An increased incidence of gastrointestinal disturbances (soft stools, mucoid stools, diarrhoea) in all treated groups compared with controls, although not strictly dose related, precluded the determination of a NOAEL. Inhibition was noted for plasma cholinesterase (at 0.05 mg/kg bw per day and above), for erythrocyte cholinesterase (marginally in males and females at 0.125 mg/kg bw per day and higher) and for brain cholinesterase (at 0.25 mg/kg bw per day in males only). Skin inflammation was noted in some dogs at 0.05 mg/kg bw per day and above, which could be associated with the low incidence of histiocytomas observed at 0.125 and 0.25 mg/kg bw per day (1/10 at each dose level).[67]

Carcinogenicity

No significant increases in the incidence of tumours of any type were reported in the two-year studies in rats conducted by Weil and Carpenter.[68,69] In an 18-month bioassay in male CD-1 mice, in which groups of 50 animals were fed aldicarb in the diet equivalent to doses of 0, 0.1, 0.3 or 0.7 mg/kg bw per day, there were no increases in the incidence of tumours related to treatment.[70] In an additional 18-month bioassay in Charles River CD-1 mice, groups of 50 animals per sex were administered aldicarb sulphone in the diet equivalent to doses of 0, 0.15, 0.6, 2.4 or 9.6 mg/kg bw per day. There was no significant difference in the incidence of tumours in the treated groups compared with controls.[71]

The National Cancer Institute[72] conducted bioassays in F344 rats and B6C3F$_1$ mice (50 per sex per dose group, 25 per sex in control group) that ingested aldicarb at 2 or 6 ppm in the diet for 103 weeks. Although numerous tumours were observed in the treated animals, there were no significant increases that could be attributed to aldicarb administration. However, as no significant differences were observed in mean body weights and mortality, administered doses in these studies may not have been sufficiently high for maximum sensitivity.

Quarles *et al.*[73] examined the transforming and tumorigenic activity of aldicarb following intra-peritoneal injections of 0.1 or 0.5 mg/kg bw of aldicarb or 2.0 mg/kg bw of the nitroso derivative of aldicarb to pregnant hamsters on day 10 of gestation. Cultured foetal cells were plated on day 13, then injected subcutaneously into young adult nude mice, which were observed for 6–12 months. Aldicarb did not induce either morphological transformants or cells that grew in agar, whereas the nitrosoaldicarb induced morphological transformants that were tumorigenic in nude mice.

Mutagenicity

Dominant lethal mutations were not induced by aldicarb or aldicarb sulphone in studies in which treated male rats were mated with unexposed females.[74,75] A significant increase in chromosomal aberrations was observed in bone marrow cells of male albino rats following intraperitoneal injection of an aldicarb: acetone solution for one or five days. The authors concluded that aldicarb may be clastogenic in rats and may have a cumulative effect, as greater numbers of chromosomal aberrations were produced by repeated treatments compared with single injections.[76] However, no chromosomal aberrations were induced by aldicarb

in another assay on rat bone marrow cells *in vivo*, with or without metabolic activation.[77]

Aldicarb induced a significant increase in sister chromatid exchange in cultured human lymphocytes, both with and without metabolic activation,[78,79] but did not cause DNA damage in human skin fibroblasts.[80] Neither aldicarb sulphoxide nor aldicarb sulphone induced mutations in Chinese hamster ovary cells with or without activation,[81–83] nor was there unscheduled DNA repair synthesis in cultured rat hepatocytes exposed to either metabolite.[84,85] Aldicarb was found to be weakly mutagenic in *Salmonella typhimurium* in the Ames test, but only without activation by liver microsomal enzymes.[36] It induced damage in a repair-deficient strain of *S. typhimurium* but not in a repair-proficient strain.[86] The results for aldicarb and aldicarb metabolites in Ames mutagenesis assays conducted by other researchers have been negative.[87–90] Aldicarb did not cause reverse mutation in *Escherichia coli* WP2 or *Saccharomyces cerevisiae*.[87,91]

Teratogenicity and Reproductive Effects

No significant effects on fertility, gestation, viability of offspring, lactation or mean litter weights and no histological effects in litters were observed in a three-generation reproduction study in CFE rats in which aldicarb was administered in the diet at doses of 0.05 or 0.1 mg/kg bw per day.[92] In a repeat three-generation study in Harlan-Wistar albino rats, there was a significant difference in the body weight of second-generation pups of the highest dose group (0.7 mg/kg bw per day).[74] Aldicarb sulphone was administered in the diet at doses up to 9.6 mg/kg bw per day in a three-generation reproduction study in Harlan-Wistar albino rats. Although the body weights of males were reduced in the highest dose group, it was concluded that aldicarb did not produce any adverse effects on reproduction in this study.[75]

Teratogenic effects were not reported in any of the three-generation studies. Cambon *et al.*[34,35] reported that single aldicarb doses of 0.001, 0.01 or 0.1 mg/kg bw per day administered by gastric intubation to pregnant Sprague-Dawley rats on the 18th day of gestation caused a significant inhibition of brain acetylcholinesterase activity, which was greater in foetal than in maternal tissues and involved different isoenzymes. No significant differences in foetal malformations or developmental variations were observed in the offspring of pregnant Dutch-Belted rabbits administered daily aldicarb doses of 0, 0.1, 0.25 or 0.50 mg/kg bw via gavage on days 7 through 27 of gestation. Although the number of viable foetuses and implantation values were less in treated groups than in controls, the values were within the normal range for historical controls.[93] Similarly, teratogenic effects were not observed in a study in which pregnant CD rats were orally administered aldicarb at doses up to 0.5 mg/kg bw per day for 10 days during gestation.[94]

Immunotoxicity and Delayed Neurotoxicity

There was an inverse dose–response relationship for the suppression of immune parameters in Swiss Webster or CF-1 mice exposed to doses of 1–1000 ppb aldicarb in drinking water for 14 or 34 days.[95] However, this relationship was not confirmed in additional 34-day studies in which adverse effects were not reported in Swiss Webster and B6C3F_1 mice drinking water containing 0.1–1000 ppb aldicarb.[96,97]

Daily intraperitoneal injections of 0.01–10 ppb aldicarb for seven days caused a 64–100% suppression in macrophage-mediated cytotoxicity to LSA tumour cells in C3H mice, but concentrations up to 1000 ppb did not alter the natural killer cell mediated cytotoxicity against NK-sensitive YAC-1 tumour cells. Macrophage-mediated cytotoxicity was suppressed to a greater degree by the repeated injections than by a single treatment, and the lowest administered aldicarb concentration produced the greatest decrease in macrophage-mediated cytotoxicity at a high ratio of effector cells to target cells.[98] The results of animal studies thus indicate that the immune response reported in the studies on humans[49,51] cannot be discounted entirely, despite the weak evidence of the studies themselves, and that further work is required on this aspect.

Neither aldicarb nor aldicarb sulphone induced delayed neurotoxicity in chickens.[99,100] Intraperitoneal injections of 0.266 mg/kg bw aldicarb and above interfered with avoidance behaviour in rats.[101] Aldicarb and aldicarb metabolites do not potentiate the effects produced by other carbamate pesticides or organophosphorus insecticides in rats or mice.[102–105]

Classification and Assessment

Aldicarb has not induced increases in tumour incidence in carcinogenicity bioassays in rats and mice and has therefore been classified by the Food Directorate of Health Canada as probably not carcinogenic to humans. For these compounds, the acceptable daily intake (ADI) is derived on the basis of division of a NOAEL or lowest-observed-adverse-effect level (LOAEL) for other toxic effects by an uncertainty factor. Although there has been weak evidence that aldicarb may be immunotoxic, the only toxic effect observed consistently in studies conducted to date is the rapidly reversible inhibition of acetylcholinesterase activity. The biological significance of changes in cholinesterase levels in humans and experimental animals has been a source of much controversy owing to a lack of concordance of plasma or blood cholinesterase

inhibition with clinical signs of disruptions in nerve transmission. There is also a significant degree of individual variation in the degree of inhibition that is manifested clinically in humans and animals.[106] Therefore, it has been difficult to establish a level of cholinesterase depression considered to be biologically significant.

The two major metabolites of aldicarb, the sulphoxide and the sulphone, are also acetylcholinesterase inhibitors, with the sulphoxide approximately equipotent with the parent compound and the sulphone somewhat less potent. Long-term exposure of laboratory animals to toxic doses of aldicarb and/or its toxic metabolites does not result in a greater toxic response than that seen after a single dose, owing to the rapidly reversible nature of the effect and the complete restoration of normal values within a few hours, usually well before additional exposure takes place. In this case, acute studies are considered to be as appropriate as longer-term studies as a basis for derivation of the ADI. The toxicity of aldicarb is dependent on the vehicle and nature of administration, possibly owing to reduced bioavailability of the compound or to the bolus effect of certain forms of administration (e.g., gavage).[107] The studies considered most appropriate for derivation of the ADI, therefore, are those in which aldicarb was administered in the diet or drinking water. The anticholinergic responses of various species of laboratory animals to aldicarb are comparable in degree to those seen in humans, based on similar NOAELs observed in dogs, rats, monkeys and humans, over acute or long-term exposure periods. Therefore, it was not considered necessary to rely on animal toxicity studies, and a new human volunteer study that included both males and females was chosen as the basis for derivation of the ADI.[47,48] In this study, a NOAEL of 0.01 mg/kg bw was determined, based on inhibition of red blood cell cholinesterase at 0.025 mg/kg bw and higher and on the occurrence of profuse sweating over the whole body, a clinical symptom of cholinesterase inhibition, at 0.06 mg/kg bw, with suggestions of this effect in the form of mild localized sweating at 0.025 and 0.05 mg/kg bw. No uncertainty factor was considered necessary as an adjustment for the acute nature of the exposure because of the transient nature of the effect and the extensive database indicating that no additional toxicity is elicited after a longer duration of exposure. Information from several series of poisonings as a result of the improper use of aldicarb indicated that susceptible populations including adolescents would be protected from any adverse effects, with some margin of safety, at the level calculated on the above basis. The ADI has therefore been derived as follows:

$$\text{ADI} = \frac{0.01 \text{ mg/kg bw per day}}{10} = 0.001 \text{ mg/kg bw per day}$$

where:

- 0.01 mg/kg bw per day is the NOAEL for red blood cell cholinesterase inhibition in the 1992 human volunteer study carried out for Rhone-Poulenc[47,48]
- 10 is the uncertainty factor (×10 for the variability observed in the human population).

Rationale

Because aldicarb is classified as probably not carcinogenic to humans, the maximum acceptable concentration (MAC) is derived from the ADI as follows:

$$\text{MAC} = \frac{0.001 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} \approx 0.009 \text{ mg/L}$$

where:

- 0.001 mg/kg bw per day is the ADI, as derived above
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of total daily intake of aldicarb allocated to drinking water
- 1.5 L/d is the average daily consumption of drinking water by an adult.

This guideline is considered to be applicable to the total of aldicarb and its toxic metabolites, aldicarb sulphoxide and aldicarb sulphone.

References

1. Food and Agriculture Organization/World Health Organization. Pesticide residues in food — 1979 monographs. No. 20 (Suppl.). Joint meeting of the FAO panel of experts and the WHO expert group on pesticide residues, Geneva (1979).

2. Royal Society of Chemistry. The agrochemicals handbook. 2nd edition (update April 1, 1988). Nottingham, UK (1988).

3. Suntio, L.R., Shiu, W.Y., Mackay, D., Seiber, J.N. and Glotfelty, D. Critical review of Henry's law constants for pesticides. Rev. Environ. Contam. Toxicol., 103: 1 (1988).

4. Environment Canada/Agriculture Canada. Pesticide Registrant Survey, 1986 report. Commercial Chemicals Branch, Conservation and Protection, Environment Canada, Ottawa (1987).

5. U.S. Environmental Protection Agency. EPA notice of preliminary determination regarding continued registrations of products containing aldicarb. Fed. Regist., 53: 24630 (1988).

6. Cohen, S.Z., Creeger, S.M., Carsel, R.F. and Enfield, C.G. Potential pesticide contamination of groundwater from agricultural uses. In: Treatment and disposal of pesticide wastes. R.F. Krueger and J.N. Seiber (eds.). ACS Symp. Ser. No. 259, American Chemical Society, Washington, DC. p. 297 (1984).

7. Lightfoot, E.N., Thorne, P.S., Jones, R.L., Hansen, J.L. and Romine, R.R. Laboratory studies on mechanisms for the degradation of aldicarb, aldicarb sulphoxide, and aldicarb sulphone. Environ. Toxicol. Chem., 6: 377 (1987).

8. U.S. Environmental Protection Agency. EPA notice initiating review of aldicarb pesticides. Fed. Regist., 49: 28320 (1984).

9. Coppedge, J.R., Lindquist, D.A., Bull, D.L. and Dorough, H.W. Fate of 2-methyl-2(methylthio) propionaldehyde O-(methyl-carbamoyl) oxime (Temik) in cotton plants and soil. J. Agric. Food Chem., 15: 902 (1967).

10. Bull, D.L., Stokes, R.A., Coppedge, J.R. and Ridgway, R.L. Further studies of the fate of aldicarb in soil. J. Econ. Entomol., 63(4): 1283 (1970).

11. Moye, H.A. and Miles, C.J. Aldicarb contamination of groundwater. Rev. Environ. Contam. Toxicol., 105: 99 (1988).

12. Lorber, M.N., Cohen, S.Z., Noren, S.E. and Buchananne, G.D. A national evaluation of leaching potential of aldicarb — part 1: An integrated assessment methodology. Groundwater Monit. Rev., 9(4): 109 (1989).

13. Jones, R.L. The aldicarb experience — 2: Results of monitoring and research programs. Revision of paper presented at the Soil Science Society of America Workshop on the Contamination of Groundwater, New Orleans, December 5–6, 1986 (1988), cited in reference 12.

14. Dierberg, F.E. and Given, C.J. Aldicarb studies in groundwaters from Florida citrus groves and their relation to ground-water protection. Ground Water (U.S.A.), 24(1): 16 (1986).

15. Union Carbide. Temik aldicarb drinking water sampling program. Unpublished data submitted to the Environmental Health Directorate, Department of National Health and Welfare, Ottawa (1986).

16. Hiebsch, S. The occurrence of thirty-five pesticides in Canadian drinking water and surface water. Unpublished report prepared for the Environmental Health Directorate, Department of National Health and Welfare, Ottawa (1988).

17. Priddle, M.W., Jackson, R.E., Novakowski, S., Deuhoed, S., Graham, B.W., Patterson, R.J., Chaput, D. and Jardine, D. Migration and fate of aldicarb in the sandstone aquifer of Prince Edward Island. Water Pollut. Res. J. Can., 22(1): 173 (1987).

18. Priddle, M.W., Jackson, R.E. and Mutch, J.P. Contamination of the sandstone aquifer of Prince Edward Island, Canada, by aldicarb and nitrogen residues. Groundwater Monit. Rev., 9(4): 134 (1989).

19. Union Carbide. Union Carbide agricultural products. Temik® aldicarb pesticide. Removal of residues from water. Research and Development Department (1979), cited in reference 28.

20. Health Canada. Pesticides rulings proposal: aldicarb (Temik). Prepared by the Food Directorate, Health Protection Branch, July (1994).

21. Hundley, H.K., Cairns, T., Luke, M.A. and Masumoto, H.T. Pesticide residue findings by the Luke method in domestic and imported foods and animal feeds for fiscal years 1982–1986. J. Assoc. Off. Anal. Chem., 71(5): 875 (1988).

22. U.S. Environmental Protection Agency. Proposed rules. Fed. Regist., 50: 219 (1985).

23. Krause, R.T. Liquid chromatographic determination of N-methylcarbamate insecticides and metabolites in crops. I: Collaborative study. J. Assoc. Off. Anal. Chem., 68(4): 726 (1985).

24. Gunderson, E.L. FDA Total Diet Study, April 1982 – April 1984, dietary intakes of pesticides, selected elements, and other chemicals. J. Assoc. Off. Anal. Chem., 71(6): 1200 (1988).

25. Zhong, W.Z., Lemley, A.T. and Spalik, J. Quantitative determination of ppb levels of carbamate pesticides in water by capillary gas chromatography. J. Chromatogr., 299: 269 (1984).

26. Maitlen, J.C., McDonough, L.M. and Beroza, M. Determination of residues of 2-methyl-2(methylthio) propionaldehyde O-(methyl-carbamoyl) oxime (UC 21149, Temik) and its sulfoxide and sulfone by gas chromatography. J. Agric. Food Chem., 16: 549 (1968).

27. Maitlen, J.C., McDonough, L.M. and Beroza, M. Rapid method for the extraction, cleanup and GC determination of toxic residues of Temik. J. Assoc. Off. Anal. Chem., 52(4): 786 (1969).

28. U.S. Environmental Protection Agency. Health advisory for aldicarb in drinking water. Rev. Environ. Contam. Toxicol., 104: 21 (1988).

29. Foerst, D.L. and Moye, H.A. Aldicarb and related compounds in drinking water via direct aqueous injection HPLC with post-column derivatization. EPA/600/D-85/051, U.S. Environmental Protection Agency, Cincinnati, OH (1985).

30. Environmental Science and Engineering. Review of treatability data for removal of twenty-five synthetic organic chemicals from drinking water. Prepared for the U.S. Environmental Protection Agency's Office for Drinking Water (1984), cited in reference 28.

31. Baron, R.L. and Merriam, T.L. Toxicology of aldicarb. Rev. Environ. Contam. Toxicol., 105: 1 (1988).

32. Andrawes, N.R., Dorough, H.W. and Lindquist, D.A. Degradation and elimination of Temik in rats. J. Econ. Entomol., 60: 979 (1967).

33. Marshall, T.C. and Dorough, H.W. Biliary excretion of carbamate insecticides in the rat. Pestic. Biochem. Physiol., 11: 56 (1979).

34. Cambon, C., Declume, C. and Derache, R. Effect of the insecticidal carbamate derivatives (carbofuran, pirimicarb, aldicarb) on the activity of acetylcholinesterase in tissues from pregnant rats and foetuses. Toxicol. Appl. Pharmacol., 49: 203 (1979).

35. Cambon, C., Declume, C. and Derache, R. Foetal and maternal rat brain acetylcholinesterase: isoenzyme changes following insecticidal carbamate derivatives poisoning. Arch. Toxicol., 45: 257 (1980).

36. Risher, J.F., Franklin, L.M. and Stara, J.F. The toxicologic effects of the carbamate insecticide aldicarb in mammals: a review. Environ. Health Perspect., 72: 267 (1987).

37. Hayes, W.J. Pesticides studied in man. Williams & Wilkins, Baltimore, MD (1982).

38. Parks, P., Lipman, J. and Eidelman, J. Carbamate toxicity. S. Afr. Med. J., 72: 222 (1987).

39. Lee, M.H. and Ransdell, J.F. A farmworker death due to pesticide toxicity: a case report. J. Toxicol. Environ. Health, 14: 239 (1984).

40. Hirsch, G.H., Mori, B.T., Morgan, G.B., Bennett, P.R. and Williams, B.C. Report of illnesses caused by aldicarb-contaminated cucumbers. Food Addit. Contam., 5(2): 155 (1987).

41. Anonymous. Aldicarb food poisoning from contaminated melons — California. J. Am. Med. Assoc., 256(2): 175 (1986).

42. Green, M.A., Heumann, M.A., Wehr, H.M., Foster, L.R., Williams, L.P., Polder, J.A., Morgan, C.L., Wagner, S.L., Wanke, L.A. and Witt, J.M. An outbreak of watermelon-borne pesticide toxicity. Am. J. Public Health, 77(11): 1431 (1987).

43. Goes, E.A., Savage, E.P., Gibbons, G., Aaronson, M., Ford, S.A. and Wheeler, W.H. Suspected foodborne carbamate pesticide intoxications associated with ingestion of hydroponic cucumbers. Am. J. Epidemiol., 111(2): 254 (1980).

44. Jackson, R.J. and Goldman, L. Aldicarb poisoning — comment. J. Am. Med. Assoc., 256(23): 3218 (1986).

45. Haines, R.G. Ingestion of aldicarb by human volunteers: a controlled study of the effects of aldicarb on man. Unpublished study, Union Carbide Agricultural Products Co. (1971).

46. Cope, O.E. and Romine, R.R. Temik aldicarb pesticide. Results of aldicarb ingestion and exposure studies with humans and results of monitoring human exposure in working environments. Unpublished study, file no. 18269, Union Carbide Agricultural Products Co. (1973).

47. Rhone-Poulenc AG Company. A safety and tolerability study of aldicarb at various dose levels in healthy male and female volunteers. Inveresk Clinical Research Report No. 7786 (1992), cited in reference 48.

48. IRIS (Integrated Risk Information System). On-line database of the U.S. Environmental Protection Agency, January (1995).

49. Fiore, M.C., Anderson, H.A., Hong, R., Golubjatnikov, R., Seiser, J.E., Nordstrom, D., Hanrahan, L. and Belluck, D. Chronic exposure to aldicarb-contaminated groundwater and human immune function. Environ. Res., 41: 633 (1986).

50. World Health Organization. Guidelines for drinking-water quality. 2nd edition. Vol. 2. Health criteria and other supporting information. Geneva (in press).

51. Mirkin, I.R., Anderson, H.A., Hanrahan, L., Hong, R., Golubjatnikov, R. and Belluck, D. Changes in T-lymphocyte distribution associated with ingestion of aldicarb-contaminated drinking water: a follow-up study. Environ. Res., 51: 35 (1990).

52. Sterman, A.B. and Varma, A. Evaluating human neurotoxicity of the pesticide aldicarb: when man becomes the experimental animal. Neurobehav. Toxicol. Teratol., 5: 493 (1983).

53. Whitlock, N.H., Schuman, S.H. and Loadholt, C.B. Executive summary and epidemiologic survey of potential acute health effects of aldicarb in drinking water — Suffolk County, N.Y. South Carolina Pesticide Hazard Assessment Program Center, Medical University of South Carolina, Charleston, SC. Prepared for the Health Effects Branch, Hazard Evaluation Division, Office of Pesticide Programs, U.S. Environmental Protection Agency (1982), cited in reference 31.

54. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances (RTECS) (1989).

55. DePass, L.R., Weaver, E.V. and Mirro, E.J. Aldicarb sulfoxide/aldicarb sulfone mixture in drinking water of rats: effects on growth and acetylcholinesterase activity. J. Toxicol. Environ. Health, 16: 163 (1985).

56. Weil, C.S. and Carpenter, C.P. Temik sulfoxide. Results of feeding in the diet of rats for six months and dogs for three months. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1968).

57. Weil, C.S. and Carpenter, C.P. Temik sulfone. Results of feeding in the diet of rats for six months and dogs for three months. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1968).

58. Weil, C.S. and Carpenter, C.P. Purified and technical Temik. Results of feeding in the diets of rats for one week. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1969).

59. Weil, C.S. and Carpenter, C.P. Temik. Results of feeding in the diets of rats for 7 days. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1970).

60. Weil, C.S. and Carpenter, C.P. Temik (T), Temik sulfoxide (TSO), Temik sulfone (TSO_2), 1:1 TSO–TSO_2. Results of feeding in the diet of rats for 7 days. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1970).

61. Weil, C.S. and Carpenter, C.P. 1:1 Temik:Temik sulfone. Results of feeding in the diet of mice for 7 days. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1970).

62. Weil, C.S. and Carpenter, C.P. Temik. Results of feeding in the diet of mice for 7 days. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1970).

63. Weil, C.S. and Carpenter, C.P. Aldicarb. Seven-day inclusion in diet in dogs. Report No. 36-33, unpublished report from Carnegie-Mellon Institute (1973).

64. Weil, C.S. and Carpenter, C.P. Aldicarb oxime (all). Results of feeding in the diet of rats for 7 days. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1974).

65. Weil, C.S. and Carpenter, C.P. Aldicarb. Inclusion in the diets of dogs for three months. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1974).

66. Nycum, J.S. and Carpenter, C.P. Toxicity studies on Temik and related carbamates. Unpublished study submitted by Union Carbide Corporation (1968).

67. Department of National Health and Welfare. Status report for aldicarb (Temik). Unpublished report, Pesticides Division, Bureau of Chemical Hazards, Environmental Health Directorate, Ottawa (1991).

68. Weil, C.S. and Carpenter, C.P. Two-year feeding of compound 21149 in the diet of rats. Unpublished report from Mellon Institute (1965).

69. Weil, C.S. and Carpenter, C.P. Aldicarb (A), aldicarb sulfoxide (ASO), aldicarb (ASO_2) and a 1:1 mixture of ASO:ASO_2. Two year feeding in the diet of rats. Unpublished report from Mellon Institute (1972).

70. Weil, C.S. and Carpenter, C.P. Aldicarb, 18-month feeding in the diet of mice, Study II. Unpublished report from Mellon Institute (1974).

71. Woodside, M.S., Weil, C.S. and Cox, E.F. Aldicarb sulphone: 18 month feeding in the diet of mice. Report No. 40-38, unpublished report from Carnegie-Mellon Institute, submitted to the World Health Organization by Union Carbide Corporation (1977).

72. National Cancer Institute. Bioassay of aldicarb for possible carcinogenicity. NCI-CG-TR-136, Public Health Service, National Institutes of Health, U.S. Department of Health, Education and Welfare (1979).

73. Quarles, J.M., Sega, M.W., Schenley, C.K. and Lijinsky, W. Transformation of hamster fetal cells by nitrosated pesticides in a transplacental assay. Cancer Res., 39: 4525 (1979).

74. Weil, J.S. and Carpenter, C.P. Aldicarb — Inclusion in the diet of rats for three generations and a dominant lethal mutagenesis test. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1974).

75. Woodside, M.D., Weil, C.S. and Cox, E.F. Aldicarb sulfone. Inclusion in the diet of rats for three generations, dominant lethal mutagenesis and teratology studies. Report No. 40-1, unpublished report from Carnegie-Mellon Institute (1977).

76. Sharaf, A.A., Temtamy, S.A., DeHondt, H.A., Belal, M.H. and Kassam, E.A. Effect of aldicarb (Temik), a carbamate insecticide, on chromosomes of the laboratory rat. Egypt. J. Genet. Cytol., 11: 143 (1982).

77. Ivett, J.L., Myhr, B.C. and Lebowitz, H.D. Mutagenicity evaluation of aldicarb technical 93.47% in the bone marrow cytogenetic assay. Report No. 22202, unpublished report from Litton Bionetics, Inc. (1984), cited in reference 31.

78. Cid, M.G. and Matos, E. Induction of sister-chromatid exchanges in cultured human lymphocytes by aldicarb, a carbamate pesticide. Mutat. Res., 138: 175 (1984).

79. Debuyst, B. and Larebeke, N. Induction of sister-chromatid exchanges in human lymphocytes by aldicarb, thiofanox and methomyl. Mutat. Res., 113: 242 (1983).

80. Blevins, R.D., Lijinsky, W. and Ragan, J.D. Nitrosated methylcarbamate insecticides: effect on the DNA of human cells. Mutat. Res., 44: 1 (1977).

81. Stankowski, L.F., Naismith, R.W. and Matthews, R.J. CHO/HGPRT mammalian cell forward gene mutation assay. Aldicarb. Report No. PH 314-UC-003-84n, unpublished report from Pharmakon Research International, Inc. (1985).

82. Stankowski, L.F., Naismith, R.W. and Matthews, R.J. CHO/HGPRT mammalian cell forward gene mutation assay. Aldoxycarb. Report No. PH 314-UC-002-84, unpublished report from Pharmakon Research International, Inc. (1985).

83. SanSebastian, J.R., Naismith, R.W. and Matthews, R.J. *In vitro* chromosome aberration analysis in Chinese hamster ovary cells (CHO). Aldoxycarb technical. Report No. OG 320-UC-005-83, unpublished report from Pharmakon Research International, Inc. (1984).

84. Godek, E.G., Naismith, R.W. and Matthews, R.J. Rat hepatocyte primary culture/DNA repair test. Aldicarb technical. Report No. PH-311-UC-005-83, unpublished report from Pharmakon Research International, Inc. (1984).

85. Godek, E.G., Naismith, R.W. and Matthews, R.J. Rat hepatocyte primary culture/DNA repair test. Aldoxycarb technical. Report No. PH-311-UC-006-83, unpublished report from Pharmakon Research International, Inc. (1984).

86. Rashid, K.A. and Mumma, R.O. Screening pesticides for their ability to damage bacterial DNA. J. Environ. Sci. Health, B21: 319 (1986).

87. Dunkel, V.C., Zeiger, E., Brusick, D., McCoy, E., McGregor, D., Mortelmans, K., Rosenkranz, H.S. and Simmon, V.F. Reproducibility of microbial mutagenicity assays: II. Testing of carcinogens and noncarcinogens in *Salmonella typhimurium* and *Escherichia coli*. Environ. Mutagen., 7 (Suppl. 5): 1 (1985).

88. Godek, E.G., Dolak, M.C., Naismith, R.W. and Matthews, R.J. Ames *Salmonella*/microsome plate test. Aldicarb sulfone. Report No. PH-301-UC-003-80, unpublished report from Pharmakon Laboratories (1980).

89. Godek, E.G., Dolak, M.C. and Naismith, R.W. Ames *Salmonella*/microsome plate test. Aldicarb sulfoxide. Report No. PH-301-UC-002-80, unpublished report from Pharmakon Laboratories (1980).

90. Godek, E.G., Dolak, M.C. and Naismith, R.W. Ames *Salmonella*/microsome plate test. Temik aldicarb pesticide. Report No. PH-301-UC-004-80, unpublished report from Pharmakon Laboratories (1980).

91. Guerzoni, M.E., Del Cupolo, L. and Ponti, I. Attivita mutagenica degli antiparassitari. Riv. Sci. Tecnol. Alimenti Nutr. Um., 6: 161 (1976), cited in reference 31.

92. Weil, C.S. and Carpenter, C.P. Results of a three generation reproduction study on rats fed compound 21149 in their diet. Unpublished report from Mellon Institute, submitted by Union Carbide Corporation (1964).

93. International Research and Development Corporation. Teratology study in rabbits. Unpublished report from Union Carbide Corporation (1983).

94. Tyl, R.W. Developmental toxicity evaluation of aldicarb technical administered by gavage to CD (Sprague-Dawley) rats. Report No. 51-551, unpublished report from Bushy Run Research Center (1988).

95. Olson, L.J., Erickson, B.J., Hinsdill, R.D., Wyman, J.A., Porter, W.P., Binning, L.K., Bidgood, R.D. and Nordheim, E.V. Aldicarb immunomodulation in mice: an inverse dose–response to parts per billion levels in drinking water. Arch. Environ. Contam. Toxicol., 16: 433 (1987).

96. Thomas, P.T. and Ratajczak, H.V. Assessment of carbamate pesticide immunotoxicity. Toxicol. Ind. Health, 4(3): 381 (1988).

97. Thomas, P.T., Ratajczak, H.V., Eisenberg, W.C., Furedi-Machacek, M., Ketels, K.V. and Barbera, P.W. Evaluation of host resistance and immunity in mice exposed to the carbamate pesticide aldicarb. Fundam. Appl. Toxicol., 9: 82 (1987).

98. Selvan, R.S., Dean, T.N., Misra, H.P., Nagarkatti, P.S. and Nagarkatti, M. Aldicarb suppresses macrophage but not natural killer (NK) cell-mediated cytotoxicity of tumor cells. Bull. Environ. Contam. Toxicol., 43: 676 (1989).

99. Johnson, H.E. and Carpenter, C.P. Temik (technical grade compound 21149). Demyelination potential in chickens. Report No. 29-90, unpublished report from Mellon Institute (1966).

100. Babish, J.G. and Salerno, A. Neurotoxicity evaluation of UC 21865 in White Leghorn hens (*Gallus domesticus*). Report No. 5233, unpublished report from Food and Drug Research Laboratories, Inc. (1977), cited in reference 31.

101. Johnson, H.E. and Carpenter, C.P. Temik (technical grade compound 21149). Comparative behavioral effect in rats. Report No. 29-90, unpublished report from Mellon Institute (1966).

102. Weil, C.S. and Carpenter, C.P. Miscellaneous toxicity studies. Report No. 33-92, unpublished report from Mellon Institute (1970).

103. Weil, C.S. and Carpenter, C.P. Temik and other materials. Miscellaneous single dose peroral and parenteral LD_{50} assays and some joint action studies. Report No. 33-7, unpublished report from Mellon Institute (1970).

104. West, J.S. and Carpenter, C.P. Temik (compound 21149, technical). Joint action with selected organic phosphate and carbamate pesticides. Report No. 29-98, unpublished report from Mellon Institute (1966).

105. Dorough, H.W. Effect of Temik on methyl parathion toxicity to mice. Tex. Agric. Exp. Stn. Prog. Rep. 2771 (1970), cited in reference 31.

106. Wills, J.H. The measurement and significance of changes in the cholinesterase activities of erythrocytes and plasma in man and animals. CRC Crit. Rev. Toxicol., 1: 153 (1972).

107. Food and Agriculture Organization/World Health Organization. Pesticide residues in food — 1982 monographs. Joint meeting of the FAO panel of experts and the WHO expert group on pesticide residues, Geneva (1982).