IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Sampling and Analytical Methods

Various complications arise in the atmospheric sampling for malathion due to its formulation as an emulsifiable liquid, wettable powder, or dust. [131]

Packed column adsorption is efficient for trapping vapors, but sample recovery from the column is difficult. [58] Filters, whether glass fiber or cellulose pad, permit passage of large volumes of air in a short time, but they have low efficiency for vapors and lose unknown amounts of both particulate and aerosol samples during the collection period. [37,92] Scrubbers are good for aerosols and vapors, but the use of sintered glass precludes particle collection. [132,133]

Miles et al [134] determined the collection efficiency of Greenburg-Smith impingers using ethylene glycol as the collection medium. They compared the amount originally present in a U-tube or a vaporization chamber to that collected in Greenburg-Smith impingers for parathion. Either the U-tube or the vaporization chamber was connected directly to two Greenburg-Smith impingers in series. The authors found that in a 240-minute sampling period, 94.8% of the parathion in the U-tube was collected by the first impinger connected to the U-tube, and 87.2% (19.8μg) of the parathion was collected by the first impinger connected to the vaporization chamber. The flowrate was not given. Miles et al [134] also determined the collection efficiency of Greenburg-Smith impingers for parathion dusts. In this study, they dispersed parathion dust in a chamber and collected the dispersed dust with three Greenburg-Smith impingers connected in series.

The flowrate again was not given. The results indicated that 99.9% (3,000μg) of the parathion dust was collected in the first impinger using ethylene glycol as the collection medium. NIOSH believes that these results are applicable to malathion as well. There is no reason to believe that the particle sizes are different, as the inert substrates for dry formulations of both malathion and parathion are the same. [135]

Culver et al [68] found that the collection efficiency of the midget impinger using ethyl alcohol as the collection medium was in excess of 90% for collecting malathion in the form of aerosolized liquid with a median diameter of 40-54 μ. No range of particle sizes within which this efficiency is applicable was given, and the method of determining the collection efficiency was not indicated. They also found that the midget impinger picked up particles of approximately the same size as did the upper respiratory tract. Since malathion may occur in air as vapor, as liquid droplets, or as an adsorbed film on solid particles, it is essential that the impinger be operated at a flowrate which will efficiently collect all forms of airborne malathion. Although no studies were found in which malathion or any other organophosphorus pesticide was used as the test compound, Roberts and McKee, [136] by comparing known concentrations of ammonia with those absorbed in midget impingers filled with distilled water, found that the most efficient air flowrate was 0.1 cu ft/min (2.8 liters/min).

Miles et al [134] investigated a variety of solvents that may be used as collection media in impingers. By varying the solvents in otherwise identical trials, they found that iso-octane, toluene, and ethyl benzene trapped parathion with high efficiency (no percentage was given), but that

losses of solvent from the impinger sampling train were high. Sampling runs longer than 30 minutes could not be made because of saturation of the system. Aliphatic hydrocarbons of higher molecular weight, including normal nonane and normal decane, formed aerosols when air was passed through the impingers, with the resultant loss of an unstated amount of solvent. The higher molecular weight hydrocarbons were difficult to evaporate. The authors found that samples of 10.7 and 205 μg were trapped with 90% or better efficiency by ethylene glycol. In comparing the collection efficiency for a known amount of parathion vapor, it was found that with ethylene glycol the collection efficiency was not dependent upon sampling time, whereas with water the collection efficiency decreased from 100% for a 10-minute sample to 52.6% for a 60-minute sample.

Thomas and Seiber [137] evaluated the solid sorbent Chromosorb 102, an alternative to liquid solvents in impingers, for the collection of malathion. Collection efficiency for the vapor of 95% technical malathion (31.5 μg malathion in a U-tube through which 9 cu m of air were drawn) in the first of two tubes, each containing 4 g of Chromosorb 102, was determined to be 102%. Upon separation of 4 g of adsorbent from a single tube into 1-g segments after sampling, no penetration of malathion vapors beyond the second segment was found. Downwind trapping of aerosolized technical (95%) malathion by Chromosorb 102-charged impingers was compared with that of similar impingers filled with ethylene glycol. Two separate runs were made, at 100 and 150 feet from the spray source, with the two types of filled impingers side by side and each with a backup impinger. Chromosorb 102 at 100 feet collected 12.3 μg and less than 0.1 μg of malathion vapor and aerosol in the first impinger and in the backup

impingers, respectively; the ethylene glycol collected only 5.5 and 0.3 μg, respectively. At 150 feet, the Chromosorb 102 impingers collected 8.6 and 0.5 μg, respectively; no data were given for ethylene glycol at this distance. Although Chromosorb 102 appears to be a superior collecting medium, the breakthrough volumes, ideal sampling rate, and precision of the method still remain to be determined.

Pending further studies, the midget impinger [68] is recommended as the air sampling method of choice. Appendix I gives details of the sampling and airflow calibration procedures to be followed when using this method. Other air sampling methods which can be shown to be equivalent, or superior, in efficiency to the midget impinger [68] with ethylene glycol as the solvent [134] may be used.

In 1964, the thermionic emission or alkali flame ionization detector was introduced by Giuffrida. [138] In 1966, Brody and Chaney [139] introduced the flame photometric detector. Both detectors are modifications of the universal flame ionization detector and are highly specific for phosphorus. Since the development of phosphorus-specific detectors, gas liquid chromatography has been the preferred method for malathion analysis. Formerly, organophosphorus pesticide analysis was done by colorimetric [140] and ultraviolet spectrophotometric [141] techniques. These, however, were highly subject to interference.

A major advantage of the gas liquid chromatography-phosphorus specific detector method of analysis is that changes in the composition, filling, and temperature of the column permit the separation of peaks due to interfering compounds from the peak of the compound of interest. These column changes result in a variation of retention times of all substances

involved. Giuffrida [138] indicated that 0.024 μg (24 ng) of parathion could be detected using gas liquid chromatography with an alkali flame ionization detector. For normal analytical work, the convenient working range for the alkali flame ionization detector was between 50 and 1,000 pg (0.05-1.0 ng) in each injection volume. With acetone as the solvent, gas liquid chromatography combined with a flame photometric detector and a 526-nm filter were reported [139] to be sensitive to 0.25 ng of malathion; the response was linear from 0.0063 to 63 ppm. Since the flame photometric detector is the more sensitive method, it is recommended over the alkali flame ionization detector. Details of this method can be found in Appendix II.

Environmental Levels and Engineering Controls

Data on environmental levels of malathion in the workplace are scanty. The only information found was contained in articles describing workers exposed while applying malathion for purposes of agricultural pest and vector control.

Wolfe et al [35] studied the dermal and potential respiratory exposures to malathion of an unstated number of air-blast sprayers and aerosol machine operators who were applying malathion spray (0.04-0.08%, 3.4 lb/acre), dust (4%, 1.4 lb/acre), or aerosol (2.5-5.0%, application rate not specified) to fruit trees or pole beans. From absorbent gauze pads attached to the workers' exposed skin areas (the face, back of neck, "V" of chest, forearms, and hands) and respirator filter pads, the authors calculated the mean dermal exposure to have been 30 mg/hour for employees spraying fruit orchards with air-blast machines, and 67 mg/hour for

employees using high-pressure hand guns. Employees using a power duster on pole beans were calculated to have had a mean dermal exposure of 23 mg/hour. Potential respiratory exposure was calculated to have been 0.11 mg/hour for air-blast orchard sprayers, 0.09 mg/hour for the high-pressure hand-gun operators, and 0.73 mg/hour for those using a power duster to dust pole beans with malathion. These results indicate a potential for much higher dermal than repiratory exposure in the application of malathion. ChE determinations were not made in this study.

Culver et al [68] studied the dermal and potential respiratory exposure to 2.5% or 5% malathion (formulating solvent not stated) of two aerosol machine operators and three field observers from the drifting aerosol cloud during mosquito control application. Cellulose head and ankle bands and a cotton knit glove on one hand of each worker were used to estimate dermal exposure. Cellulose filter pads in front of the cartridge of toxic dust respirators were used to measure potential respiratory exposure. Atmospheric sampling in the breathing zone was done with all-glass midget impingers, with ethyl alcohol as the collecting medium. Exposures were intermittent and generally brief, lasting from 20 seconds to about 30 minutes, for a total of about 5 hours during a 2-week period. The atmospheric concentration, as determined from 145 samples taken at the same time as the dermal and respiratory samples, ranged from 0.52 to 7.70 mg/cu m, depending on application distances (10-75 yards). The jeep driver received the highest dermal exposure, 32-86 mg, of which more than 90% was deposited on the hands. The total potential respiratory dose range for the 2-week period was 11-21 mg, also from the jeep driver's samples. Erythrocyte and plasma ChE activities were measured by a microadaptation of

the Michel method. [61] Either two or three preexposure examinations and daily examinations during the 2-week application period were performed. The authors concluded that slight decreases observed in ChE activities were insignificant.

Caplan et al [37] measured the potential dermal and repiratory exposures of individuals who worked outside during a 2-week mosquito control project in which malathion was applied intermittently by aerosol machines. Dermal exposure was estimated from cellulose pads attached to various parts of the body, and respiratory exposure was calculated from atmospheric concentrations of malathion collected at several points during and again 1 hour after spraying. The authors found atmospheric concentrations of malathion as high as 0.67 mg/cu m. Skin exposure ranged from 0.45 to 2.62 μg/sq cm for a man working outdoors during the spraying operation. No ChE activities or other measurements of response were reported.

Jegier [36] measured the dermal and respiratory exposures of 52 individuals who operated tractor-driven, air-blast sprayers during application of insecticides to fields of grain and vegetables. Spray formulations consisted of malathion alone as well as mixtures of malathion and DDT. Malathion was applied in a concentration of 2 lb of 25% wettable powder/100 gal of water. Respiratory exposures were estimated from analysis of breathing-zone air samples and from respirator filter pads. Dermal exposure estimates were based on the amount of insecticide found on absorbent patches taped to the forehead and wrists of observers riding beside the tractor operator. In all, the exposure of four operators to malathion was estimated. Breathing-zone samples had a range of 0.41 to

0.76 mg/cu m, with a mean of 0.59 mg/cu m. The mean respiratory exposure dose was found to be 0.08 mg/hour of malathion (range, 0.03-0.13 mg/hour) and the mean dermal dose was 2.5 mg/hour (1.5-4.9 mg/hour). The authors did not report any signs or symptoms of malathion poisoning, nor did they report any ChE activity determinations.

Good industrial hygiene requires that adequate engineering controls and work practices be used, including personal protective equipment and, under certain conditions, respiratory protection. Exhaust systems are needed at loaders, blenders, mixers, mills, packaging equipment, and all other possible sources of vapor, spray, or dust containing malathion. Liquid and dust exhaust systems must be so designed that the health of employees and that of people or animals in the surrounding community is not endangered. Dust exhaust systems should be vented into a dust collector, not into the atmosphere. Guidance for design of a ventilation system can be found in Industrial Ventilation--A Manual of Recommended Practice, [142] or more recent revisions, and in ANSI Z9.2-1971. [143] Exhaust air should not be recirculated and should be scrubbed to prevent pollution of the outdoor air. Respiratory protective equipment is not an acceptable substitute for proper engineering controls, but should be available for emergencies and for nonroutine maintenance and repair purposes.

Biologic Evaluation

Indicators of response to absorption of malathion which have been reported include: determinations of erythrocyte and plasma ChE activities, [25] electromyography, [144] electroencephalography, [145] and direct measurement of serum malathion levels. [40] With additional study,

electromyography and electroencephalography eventually may prove to be useful diagnostic tools. Direct serum malathion measurement is of extremely limited use, as the compound disappears rapidly from the blood. Only one case report [40] was identified in which this phenomenon was examined. Although serum malathion levels were found to be zero 4.5 days after ingestion of the compound, the patient remained critically ill and died 1 day later. Estimation of circulating erythrocyte and plasma ChE activities is the most effective method for monitoring occupational exposure to malathion, as reduction of ChE activity has been found consistently in clinical cases of malathion poisoning and has been far more extensively studied and documented than either of the other two examinations. Also, plasma and erythrocyte ChE activities are related generally to the severity of acute poisoning. NIOSH recommends only erythrocyte ChE monitoring as an effective measure of acute or chronic exposure. However, as plasma ChE activities are often electively monitored as well, both parameters will be discussed, and analytical methods for both are given in Appendix IV.

DuBois [146] examined the relationship between the lethal effects of six organophosphorus pesticides and their respective abilities to inhibit ChE in rat serum, liver, and brain. The numbers of animals were not specified. He found that the correlation between lethality, as reflected by the ip LD50 in rats, and inhibition of brain ChE were much better than the correlation between the ip LD50 and serum or liver ChE inhibition. Freedman et al, [147] in 1948, studied the relationship between the severity of symptoms and inhibitions of erythrocyte and plasma ChE's in 94 adult male rats weighing 125-175 g and divided into groups of 20-25 each

for single subcutaneous injections of either 1 or 2 mg/kg di-isopropyl fluorophosphate (DFP) in saline. Signs were graded as severe (marked spontaneous trembling of the body, great hyperreactivity on tapping of the spine, varying degrees of muscular weakness culminating in paralysis, and excessive salivation), moderate (intermittent periods of trembling, marked motor restlessness, moderate hyperreactivity on tapping of the spine, and spontaneous fasciculations of the muscles in the flanks), or slight (transient fasciculations while standing erect on their hindlegs and motor restlessness). Brain, plasma, and erythrocyte ChE activities were measured manometrically, and control values were obtained from 17 normal rats for these same parameters. Correlation between clinical signs and brain ChE activity was consistently significant at the 1% level. Erythrocyte ChE activity correlated less well with severity (2-5% significance), and plasma ChE activity only with severe signs (by classification). In the presence of toxic signs, erythrocyte and brain ChE activities remained closely parallel, and the correlation coefficient of erythrocyte with brain ChE was found to be 0.7 after a 1.0-mg/kg dose of DFP. Therefore, erythrocyte ChE activity seems to serve more accurately than that of plasma to approximate ChE activity in the brain in both the acute and recovery phases. The authors [147] pointed out the importance of the rapidity with which ChE activity in the circulating blood is lowered as an indicator of the severity of poisoning by organophosphorus compounds.

In a discussion of clinical case reports of organophosphorus poisoning in humans, Namba et al [49] stated that, for diagnostic purposes, estimation of erythrocyte ChE (AChE) activity was preferable because it indicated the degree of inhibition of synaptic ChE, ie, the extent of

inhibition directly determining the degree and visible manifestations of poisoning. Also, as observed in one of the cases described, following pralidoxime administration, erythrocyte ChE indicated the effectiveness of pralidoxime; plasma or serum ChE indicated the prior presence of ChE inhibition even after restoration of erythrocyte ChE activity by pralidoxime. They [49] reported that manifestations of acute poisoning in humans generally accompanied serum ChE inhibition of 50% or more. The ranges of serum ChE activity were 20-50% of normal in mild poisoning, 10-20% of normal in moderately severe poisoning, and less than 10% of normal in severe poisoning. Gage [148] pointed out that, while the inhibitory action of parathion and certain other organophosphorus compounds was more marked on the plasma enzyme than on the erythrocyte enzyme, various other organophosphates, notably the dimethyl esters, inhibited the erythrocyte enzyme first. Clinical case reports detailed in Chapter III [19,24,25,27,39,40] have all indicated that symptomatic malathion intoxication in man, irrespective of dose or route of entry, was characterized by profound inhibition of circulating ChE's, as determined by laboratory measurement. Where both erythrocyte and plasma ChE activities were determined, both were clearly depressed [25,39,40]; and where either erythrocyte or plasma ChE activity was examined, depression was uniformly evident. [19,24,27] The consistent presence of this phenomenon in malathion poisoning, no matter which blood fraction was examined, reinforces the case for measurement of ChE activity as a clinical diagnostic test in cases of possible malathion poisoning.

Frawley et al [86] found that diets containing malathion at concentrations up to 250 mg/kg of body weight inhibited ChE activity in the

erythrocytes of three dogs without significantly altering the activity of plasma ChE. Crowley and Johns [19] described a case of malathion ingestion in which erythrocyte ChE activity was reduced to less than 10% of normal during the first 7 days after ingestion and rose gradually (at the rate of about 1%/day) to 66% of normal 56 days after ingestion.

Initially, biologic assays were used to measure ChE activity. [149] Now outmoded, they have been replaced by methods classified as manometric, titrimetric, electrometric, colorimetric, radiometric, and chromatographic.

Witter [150] stated that the Warburg manometric technique, based on the measurement of carbon dioxide released when acetic acid reacts with bicarbonate, was one of the most accurate and versatile ChE measurement methods. Such techniques, however, are unsuitable for use with large populations because they require bulky apparatus and time-consuming procedures.

Methods of determination wherein ChE activity is indicated by discernible color changes have been described. The method of Limperos and Ranta [151] required only a very small blood sample; the authors found it reasonably accurate and reproducible away from the laboratory. Others who described modifications of such methods were Davies and Nicholls [152] who modified the Limperos and Ranta technique; Fleischer et al [153] who altered the Davies and Nicholls' modification; and Gerarde et al [154] who modified the procedures described by Wolfsie and Winter, [155] Limperos and Ranta, [151] and Hestrin. [156] All such methods are less accurate because the solutions used are not buffered, but they may be applicable for field screening use.

Spectrophotometric methods have been described by Ellman et al [157] and Garry and Routh, [158] and by Dietz et al, [159] who modified the Garry and Routh method.

Baum [160] reported on a method utilizing a liquid membrane electrode highly selective for ACh that correlated well with Hestrin's method. [156] Descriptions of a variety of other methods of ChE activity determination have included titrimetry by Jensen-Holm et al [161]; specially impregnated test papers which yield an obvious visible result to be matched against standard colors by Oudart and Holmstedt [162]; radiometry by Winteringham and Disney [163-165]; and gas liquid chromatography by Cranmer and Peoples. [166]

The most widely used electrometric method has been that of Michel. [61] The Michel method, which utilizes readily available apparatus, depends on measurement of the activity of H+ ions released from acetic acid produced by the catalytic action of ChE in the hydrolysis of ACh. The change in the pH of a standard buffer resulting from the enzymatic activity during a definite period of incubation at 25 C is measured by a glass electrode and associated pH meter. The pH range of 6-8 was found to be appropriate for the change in ChE activity which one would expect to find in malathion poisoning. The method was applicable to both erythrocytes and plasma, with different buffers and certain variations in technique. Michel concluded that the electrometric pH method was preferable to the manometric method because of its simplicity, minimal equipment requirements, and capacity for processing a large number of determinations in a relatively short (less than 1 minute/reading) time. It should be noted that a 1974 report by Ellin and Vicario [167] showed that, when measured by the Michel

method, [61] ChE levels varied with changes in temperature. A change of 1 degree from the 25 C prescribed by Michel resulted in a 5.5% change in plasma ChE activity and in a 3.9% change in erythrocyte ChE activity, whether or not the enzyme was inhibited. It is, therefore, necessary to carefully control temperatures when using this method. Wolfsie and Winter [155] developed a micromodification of the sampling technique used in the Michel method which was as accurate as the original.

Witter et al [168] presented a modification of the Michel method. [61] Theirs eliminated the initial pH reading, the enzyme reaction being started by adding a mixture of buffer and ACh to the diluted sample. The results are identical to those obtained with the Michel method, but twice as many samples can be analyzed in the same period.

It has been accepted generally that electrometric methods (in which delta pH is measured) and colorimetric methods are the preferred methods for measuring ChE activity because they utilize less expensive equipment and require less expertise for their operation. As colorimetric methods are subject to decreased accuracy by solution turbidity, such as would occur with erythrocytes, these methods can only be used to measure plasma ChE activity. An electrometric method is therefore recommended, specifically Wolfsie and Winter, [155] a microadaptation of the Michel method. [61] It is presented in Appendix IV.

The establishment of normal values for plasma and erythrocyte ChE in humans has become increasingly important as the use of organophosphorus pesticides has become more widespread. Therefore, a range of normal values for comparison with ChE activities in potentially exposed people has become a necessity.

Several studies in which normal ChE activities were determined have been reported. These ranges are given in Table XII-2. Further data may be found in Appendix IV. Pearson et al [169] calculated formulae to convert delta pH values to international enzyme units. These were given as: μM/ml/min = 23.15 delta pH/hr - 5.805 for erythrocyte ChE; and μM/ml/min = 3.26 delta pH/hr + 0.15 for plasma ChE.

Vorhaus and Kark [170] determined the serum ChE in 120 healthy individuals for whom the range of activity was 0.58-1.37 delta pH/hour. Fremont-Smith et al [171] reported mean serum ChE activities of 0.95 delta pH/hour for 20 "normal" men and of 0.78 delta pH/hour for women. Wolfsie and Winter [155] tested 255 healthy men and reported ranges for plasma and erythrocyte ChE values of 0.408-1.652 and 0.554-1.252 delta pH/hour, respectively. Callaway et al [172] studied a group of 247 healthy adults, 66 of whom were women, and concluded that "sex, age, occupation, and season are without effect upon the level of plasma enzyme."

Sidell and Kaminskis [173] studied the temporal variation of plasma and erythrocyte ChE activity, as opposed to laboratory-induced artifact. Eight female and fourteen male volunteers, aged 23-67, were tested biweekly throughout 1 year for ChE activity and simultaneously questioned on their medications, illnesses, alcohol intake, and exposure to ChE inhibitors. The average test period attendance was 23 times, and no subject was present every time. Nine healthy soldiers, aged 19-24, had blood drawn each working day for 3 weeks and completed questionaires similar to those of the aforementioned subjects. No correlation was obtained between ChE activity and age. A significant difference (P less than 0.01) was obtained in plasma ChE activity between men and women, but no seasonal variation in

enzyme activity was noted for either sex. Six subjects handled organophosphates. One volunteer, who had hung insecticide strips at home, experienced a 20% decrease in plasma ChE during the subsequent 6 weeks. The coefficient of variation for plasma ChE was reported to be about 6% for both sexes, with a mean of 25.7% for men and 24.3% for women.

Erythrocyte ChE activities in this study [173] were reported to be more constant, with an average coefficient of variation of 4.1%/single subject, 2.1% for men, and 3.1% for women. The average range of variation of erythrocyte ChE activity was ± 7.9% for men and ± 12.0% for women.

During the course of this study, measurements were made of packed cell volume, hemoglobin content, erythrocyte counts, mean corpuscular volume, erythrocyte ChE activity/unit volume, and ChE activity/erythrocyte. All of these were reported to vary more than the overall erythrocyte ChE activity above.

In a population studied twice at 1-year intervals, [173] the average change in plasma ChE was 9.3% for men and 16.5% for women. Changes in erythrocyte ChE activity of 6.3% for men and 6.7% for women were found at this same time. The results of this study [173] serve to vindicate the method employed as reliable within the demonstrated limits of temporal variation for this small sample. The nine control subjects, who were reported to have engaged in strenuous physical exercise, with occasional heavy drinking during the evenings, exhibited a maximum difference of 5.13% in erythrocyte and 12.8% in plasma ChE activity over the 3-week observation period.

Plasma ChE reportedly has been depressed by a variety of conditions unrelated to exposure to chemical anticholinesterase agents. Such

conditions include, but probably are not limited to, liver diseases (such as hepatitis and cirrhosis), [174] cachexia, [174] pregnancy, [175] malignant neoplasia, [175,176] pulmonary tuberculosis, [175] anemia, acute infections and chronic debilitating disease, and malnutrition. [170] Familial incidence of low plasma ChE activity was reported by Lehmann and Ryan [177] and by Kalow [178] and subsequently found to be related to the presence of an atypical gene. [179] About 1 in 5,000 healthy Canadians was found to be homozygous for this autosomal allele [178] and to have a genetically determined deficiency in plasma ChE. Heterozygotes were reported to have a mixture of normal and abnormal serum ChE. The frequency for the abnormal gene in a healthy population was reported to be 0.019 ± 0.002. [180] The importance of these observations to susceptibility to organophosphorus pesticide poisoning does not appear to have been determined. However, in interpreting the results of ChE activity tests, it is necessary to consider the above-noted factors which could cause deceptively low activities.

The activity of erythrocyte ChE has been depressed by certain pulmonary and extrapulmonary cancers [175] and in paroxysmal nocturnal hemoglobinuria. [181] Familial asymptomatic reduction in erythrocyte ChE activity has also been reported. [182]

Drugs, such as caffeine and related xanthine compounds, [183] chloroquine and other antimalarial drugs, [74] chloroform, [184] ether, [184] narcotic analgesics such as morphine and codeine, [76] and thiamine [185] have been shown to depress the activity of serum (ie, plasma) ChE activity. A few drugs have been reported to depress erythrocyte ChE activity, including quinine, [74] other antimalarial drugs, [74] and echothiophate. [186]

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The American Conference of Governmental Industrial Hygienists' (ACGIH) recommendation of a threshold limit value (TLV) for malathion of 15 mg/cu m was published in 1962. [187] A TLV of 10 mg/cu m was recommended in 1971 in a general reduction of the TLV's for "nuisance" dusts. [188] The TLV remained at that figure in 1975, without indication of an intended change in 1976. This TLV was based on studies both in experimental animals and in humans. The Documentation [188] cited the review of Johnson et al [189] in which the authors concluded that in animals, malathion was not more than 1/100 as toxic as parathion. The report of Tousey [190] was cited in support of this opinion, as was the work of Hazleton and Holland, [10] which showed little or no inhibition of blood or brain ChE activity and no other injury to rats fed malathion at a concentration of 200 ppm for 2 years. The authors of the Documentation suggested that this animal exposure was equivalent in humans to 350 mg/day. However, they did not present the assumptions underlying this estimate.

Studies in humans cited in support of the 10-mg/cu m TLV include those by Culver et al, [68] Golz, [56] Rider et al, [191] and Hayes et al. [32] The ACGIH TLV Documentation [188] reported that Culver et al [68] found that "a group of entomologists with a maximal exposure of 5 hours at a peak of 56 mg/cu m and an average of 3.3 mg/cu m had normal ChE levels." The study group consisted of two entomologists, and the exposure period comprised multiple 20-second to 30-minute exposures which totaled 5 hours during a 2-week period. With reference to the aerosol studies of Golz,

[56] the ACGIH committee wrote that "groups of 4 men each received 84 one-hour exposures in 42 consecutive days at dosages of 0, 0.15, 0.6, and 2.4 g of malathion/1,000 cu ft (5.3, 21.2, and 84.8 g/cu m)." In this study, the malathion was dispersed as an aerosol into the exposure room air in a single application. The amount released was calculated to be sufficient to produce an initial peak concentration at the stated level. No additional malathion was released into the air during the 1-hour exposure period. Since the air concentration of aerosol had probably decreased by an unknown and undeterminable amount during the 1-hour exposure period, the actual dose received by the subjects cannot be calculated. The subjects did not manifest cholinergic signs or symptoms, nor did they exhibit dose-related changes in blood ChE activities.

The dermal exposure studies of Hayes et al [32] found that men exhibited no significant decreases in blood ChE activity when exposed 5 days/week for 8-16 weeks to malathion-containing dusting powder to an extent sufficient to lead to urinary excretion of malathion-derived materials extractable from acidified urine by ethyl ether equivalent to about 48 mg of malathion/day. Since the ether-extractable phosphates represent about 69% of the total urinary metabolites, the data suggest dermal absorption of malathion of about 78 mg/day. The preliminary investigations of Rider et al [191] found no effect on blood ChE activities when malathion was fed to human volunteers for a total of 88 days as follows: 47 days at a dose of 16 mg/day alone, followed by 41 days with the same dose of malathion and 3 mg/day of EPN, a synergist of malathion.

The present federal standard for occupational exposure to malathion is 15 mg/cu m as a TWA limit (29 CFR 1910.93, published in the Federal

Register 39:23543, June 27, 1974). The American National Standards Institute (ANSI) has made no recommendations for a malathion standard to date. Foreign standards for malathion listed in 1970 by the International Labour Office (ILO) [192] were given as 0.5 mg/cu m for Bulgaria and the USSR and 15 mg/cu m for Finland, Yugoslavia, and Rumania. The scientific bases for these standards are not known to NIOSH. The ILO publication [192] gave the standard for malathion in the Federal Republic of Germany as 15 mg/cu m and stated that it was based on the 1966 Documentation on Threshold Limit Values of the ACGIH.

Basis for the Recommended Standard

As shown by the case reports in Chapter III, [19,20,23-25,27,39] the main signs and symptoms of malathion intoxication are increased bronchial secretion and excessive salivation, [19,20] nausea, [27] vomiting, [25] excessive sweating, [23] miosis, [24,39] and muscular weakness and fasciculations. [20] These signs and symptoms are induced by the inhibition of functional AChE in the nervous system. [1,2]

Malathion has been responsible for a number of nonoccupationally related cases of human poisoning, many of which have been fatal. [22,39,50,188] All known reports of such fatalities in humans have involved ingestion of large quantities of malathion, mainly in attempted suicide. [22,39,50] In the adult human, the approximate lethal oral dose can be estimated to be of the order of 0.4-1.0 g/kg based on case reports of ingestion. [19,20,25,44-46] Only extreme emergency measures, including massive therapy with atropine and 2-PAM and extensive artificial life-support systems over prolonged time periods, managed to save these

patients. Serious poisoning by dermal exposure has been reported in a few isolated instances. [27]

Only a few instances of occupationally related poisonings have been documented. [17,38,42,182] Following heavy dermal exposure to malathion for 3 or more days, applicators experienced mild-to-moderate intoxication with typical signs of inhibition of ChE. [182] In the carefully controlled experiments of Hayes et al, [32] repeated daily dustings of the entire body for 8 or more weeks with a 10% talc formulation of malathion did not produce any signs or symptoms of ChE inhibition. Liquid preparations of malathion, either as technical grade or as formulations, probably represent more pronounced dermal hazards than a 10% talc formulation. Protection for the worker can be achieved by wearing protective clothing while handling or applying malathion. Following dermal exposure to large amounts of malathion from splashes and spills, the skin should be cleansed to prevent further absorption of the material.

The study by Culver et al [68] of workplace exposure under field conditions revealed a maximum mean atmospheric concentration of malathion of 7.70 mg/cu m at a 10-yard distance from the source of the spray. The jeep driver, who had the greatest total dermal exposure, formulated the insecticide from technical grade malathion and transferred all the material from mixing cans to the aerosol rigs. The exposure was intermittent over a 2-week period. His minimum total dermal exposure was in the range of 32-86 mg (calculated as 0.5-1.23 mg/kg by the authors) over a total of 5.23 hours comprising 23 separate runs. Of this exposure, 84-93% was determined to be on his hands. Total respiratory exposures for the same jeep driver were measured at 11-21 mg over the same time span. Measurement of his

erythrocyte and plasma ChE activities revealed maximum decreases of 19 and 27%, respectively. No symptoms were reported other than "some signs of generalized fatigue," attributed by the authors to the work schedule. Since the exposure was intermittent during 2 weeks, spontaneous recovery of the ChE activity may have occurred. The authors [68] also calculated that, from the highest integrated total exposure during a month on a 40-hour workweek basis, without protective clothing, skin exposures of 17-45 mg/kg would have occurred.

A study by Jegier [36] of exposures to malathion during field-spraying operations reported a mean air concentration of 0.59 mg/cu m in the breathing zone of the tractor operator (a range of 0.41-0.76 mg/cu m). The mean rates of exposure of workers were 2.5 mg/hour by dermal contact and 0.8 mg/hour by the respiratory route. The maximum rate of exposure, both respiratory and dermal, was calculated as 5.03 mg/hour, according to the procedure described by Durham and Wolfe. [133] Jegier's procedure was based on comparisons between the measured respiratory and dermal exposures and the animal toxicities given in Clinical Memoranda on Economic Poisons. [193] No toxic effects were noted in the workers examined, although it was reported that 85% of the operators disregarded safety precautions and usual working procedures.

Studies by Weeks et al [83] demonstrated no effects on ChE activity levels in either rabbits or quail exposed for one 6-hour period to aerosols of technical malathion (95% pure) at 65 mg/cu m. ChE activity was significantly reduced when the rabbits were exposed to malathion at a concentration of 125 mg/cu m for 6 hours. The mass median diameter of the aerosolized particle was 12μm. The total amount of malathion absorbed

under these experimental conditions cannot be estimated. While the data indicated that extremely high concentrations of malathion aerosols can be tolerated by rabbits for 6 hours, it is not possible to draw any conclusions from this study about the effects on humans of repeated exposures at low concentrations.

In view of the low vapor pressure of malathion (0.00004 mmHg at 30 C, 0.05 ppm), concentrations of malathion in the workplace can exceed the current environmental limit only when significant amounts of aerosols and dusts are present. The current environmental limit is consistent with the standard for protection against physical irritation initiated by the presence of physical matter. The present federal standard for malathion in the air of the workplace is 15 mg/cu m as a TWA limit (29 CFR 1910.93). The few reported cases of occupational poisoning have resulted from violation of sound work practices. [17,38,42,182] The toxicologic evidence [17,32,36,42,68,83] suggests that the current standard provides an adequate margin of safety for the worker. Therefore, NIOSH recommends that the current workplace TWA limit be maintained.

While it is unlikely that poisoning will occur because of occupational exposure, the possibility does exist for it to occur in extreme circumstances. Case studies by Namba et al [49] have indicated that toxic effects caused by malathion appear when ChE activity is reduced to 50% of baseline. It is recommended that workers exhibiting erythrocyte ChE inhibition to 60% of baseline be removed from their jobs until recovery to 75% of baseline is observed, and that, if any worker's erythrocyte ChE is found to be reduced to 70% of baseline, an immediate evaluation of work practices be undertaken to determine that they are properly observed.