

USE OF BIOLOGIC MONITORING DATA FROM PESTICIDE USERS
IN MAKING PESTICIDE REGULATORY DECISIONS IN CALIFORNIA

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HS-1410 August 28, 1987

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USE OF BIOLOGIC MONITORING DATA FROM PESTICIDE USERS IN MAKING PESTICIDE REGULATORY DECISIONS IN CALIFORNIA. K.T. Maddy, R.I. Krieger, Linda O'Connell, Margaret Bisbiglia and Sheila Margetich. California Department of Food and Agriculture, 1220 N Street, Sacramento, CA 95814.

Exposure of users of pesticides containing active ingredients which have the potential of causing adverse effects, especially those of subchronic and chronic types, has to be accurately measured in order to make meaningful risk mitigation determinations. Acceptable methodology is usually available to measure inhalation exposure, however, most pesticide exposure is dermal. Analysis of residues on cloth pads that had been on various parts of the body may provide an overestimate of dermal exposure. Availability of dermal absorption-rate data in rodents is useful, but at least on some chemicals it is more likely to overestimate exposure than such studies done on humans or other primates. The most useful data results from development of metabolism data in humans or a suitable test animal with appropriate pharmacokinetics, including excretory data, and then biologically monitoring blood, urine, saliva or feces of persons working with the chemical under normal use conditions. Results of recent measurements of mixer/loader/applicator and hand harvest worker exposures to captan in strawberry fields included dislodgeable residues, dermal dosimetry, and urine monitoring. The latter work substantially reduced earlier human exposure estimates. Such data are used to reach safety and regulatory decisions. The goal is to avoid an inaccurate estimate of exposure that can result from some current methods of exposure assessment.

Presented at: Symposium on Biological Monitoring and Percutaneous Dermal Absorption Studies in Estimating Human Dosimetry of Pesticide Exposure at the August 30 - September 4, 1987 Meeting of the American Chemical Society in New Orleans.

DISCUSSION

In two previous reports the kinds of worker exposure data needed by California have been described in: "Pesticide Safety Program of The California Department of Food and Agriculture Based Upon Measurements of Potential Workplace Exposure and the Elimination of Excess Exposures"(1), and "Risk Assessment of Excess Pesticide Exposure to Workers in California" (2). California in its Department of Food and Agriculture (CDFA) has a more restrictive pesticide regulatory program than the U.S. Government or of any other state in the United States. California also requires more basic toxicology data and exposure data than the U.S., both on new requests for registration as well as for an extensive reregistration and reevaluation program which is now underway. More than 13,000 products are currently registered on an annual basis which contain almost 1000 active pesticide ingredients and almost 1000 chemicals which are "inert" as pesticides but which may be quite toxic to man.

Since 1971, new California laws have emphasized requirements for assessing workplace hazards for pesticide users (including long-term exposure hazards) and ways of mitigating these hazards. This has resulted in specific California requirements for data which may be used to estimate the extent of such hazards.

California's Program

The pesticide worker safety program of CDFA requires the presentation and consideration of data on : 1) pesticide vapors, mists, or dusts in the breathing zone of exposed persons; 2) pesticide dusts, powders or liquids on the skin of persons mixing, loading, and/or applying pesticides; 3) pesticide residues, including the more toxic breakdown products, on foliage and in soil of fields where work is to take place which may later contact skin; and, 4) residues in the air, on floors, counters, etc., following application of pesticides indoors.

These measurements are of value in designing methods to reduce exposure of all persons such as commercial agricultural applicators, but also including all other persons who use pesticides in non-agricultural settings. CDFA evaluates basic toxicology data, exposure measurements and the manner in which the pesticide product is to be used. By modifying the way the pesticide is to be used, establishing reentry intervals, or suggesting changes to EPA of precautionary statements on pesticide labels (which they then agree to make), the risk of exposure to a potentially hazardous pesticide may be greatly reduced.

In the past, a major difficulty in making hazard assessments for any persons who might be exposed before, during, and after a pesticide application was the lack of information on the amount of pesticide that might be inhaled or might reach the skin, the rate and amount of dermal absorption, the rate and pathway of biotransformation, and the route and rate of elimination from the body.

Some of the data that may be required by CDFA to assist in making exposure estimates of persons in various activities involving the use of pesticides include: indoor exposure; field reentry exposure; mixer, loader, and applicator exposure, metabolism, dermal absorption rate, dermal dose

response data and biological monitoring data.

Indoor Exposure

Products to be used indoors such as in (houses, apartments, offices, other institutions, and greenhouses may have exposure (inhalation, dermal, and ingestion) hazards both during the application and upon reentry. An appropriate ventilation period may be needed to protect residents, inhabitants, or workers in the treated area from inhalation of hazardous chemicals in addition to mitigations measures directed at dermal contact of excess residues on carpets, furniture and countertops.

Field Reentry

Certain pesticides pose a potential hazard to field workers if they enter a treated area and have significant contact with treated plants or soil.

The following is a guide used by CDFA in deciding if reentry data is needed.

Such data will be needed if the product is to be applied to a commercially grown crop, particularly to its foliage or the soil, and cultural practices (such as pruning or harvesting) of that particular crop involving substantial body contact with the foliage, bark, or soil, or exposure to pesticide residues shaken from the foliage or bark, and the product contains: (a) a cholinesterase inhibitor; or (b) a significantly toxic principle that can cause a detrimental acute systemic toxic reaction or is suspected of causing a chronic effect, and may be readily absorbed through the skin or inhaled following exposure to pesticide residues contacted while conducting usual cultural practices; or (c) a chemical which causes a significant primary skin irritant reaction in appropriate test animals or man; or (d) a chemical which is a significant skin sensitizer in appropriate test animals or man.

Reentry (safe waiting period) intervals are now established on the basis of: (1) data on dermal absorption rates or dermal dose response rates; (2) inhalation and dermal acute toxicity studies in animal models; (3) foliar and soil residue and dissipation rate data; and, (4) available human exposure data.

In the past, acute toxicity was the major reentry concern; more recently subacute and chronic toxicity has been a major concern.

Mixer, Loader, Applicator Exposure

Unless the acute and chronic toxicology data on the formulated product indicates negligible toxicity and risk, mixer, loader and applicator exposure data is needed, at least on the use most reasonably expected to give the most risk.

In order to make an appropriate hazard assessment, information is needed on the amount of pesticide that may be inhaled, and/or reach the skin and more importantly the amount being absorbed during and subsequent to a "typical" application.

Metabolism Data

Complete metabolism data in mammals is needed in order to understand the distribution and excretion of the pesticide and its breakdown products. Usually radiotracer studies in rodents are provided to define metabolic pathways. Greater attention needs to be given to defining pathways in accidentally or unintentionally exposed humans. Such data would establish a better experimental basis for biological monitoring.

Dermal Absorption Rate Or Dermal Dose Response Rate

Dermal absorption data usually developed in rats or monkeys are needed in the risk assessment of field workers, mixers/loaders, applicators, flaggers and other users; these data may also be used in the development of reentry intervals. The data provides information to calculate how much of the chemical enters the body after it comes into contact with the skin.

Biological Monitoring

Data collected on the amount of pesticide that falls on the skin, when used along with the animal dermal absorption rate or dermal-dose-response data often overestimates actual exposure. Metabolism data is used to determine pharmacokinetic and excretion parameters. For example if a parent chemical or a urinary metabolite can be characterized and tested for, then the amount of the chemical in urine of users can be monitored. At the same time, the amount of chemical that might be inhaled and the amount that falls on the skin can also be measured. With such data a much more objective assessment can be made of the actual exposure; use of such data may justify safe use even though dermal exposure data and the animal study dermal absorption rate data might signal an unacceptable hazard. We have previously summarized biological monitoring data on about 50 pesticide active ingredients 3.

Hazard Identification Exposure Assessment And Risk Characterization

The CDFA conducts its hazard evaluation process based on the consideration of the following factors:

1. Review of the basic toxicology data submitted by the registrant;
2. Review of other toxicology data available to CDFA (journal articles, unit studies, computerized national data banks, texts, etc.);
3. Human illness information developed by CDFA or others involving the pesticide under consideration or similar pesticides;
4. Available exposure data on this pesticide or this class of pesticides developed by CDFA or any other group; and,
5. Work practices known about or expected in California for the proposed use.

A hazard evaluation differs considerably from a basic toxicology review. For example, a specific pesticide can be found in the toxicology review to be extremely toxic; however, in the hazard evaluation process, it may be determined that the product is to be used in such small quantities with specialized equipment that a person could only be overexposed in the unusual case of equipment failure. On the other hand, a product could be found to be of low toxicity; but, the most common use might involve long hours of exposure to many workers in orchards while using hand-held spray wands spraying the pesticide above their heads with no protective clothing, due to lack of specification in the precautionary label statements. In another example, the basic toxicology data for a product may only indicate a moderate toxicity; however, in assessing the proposed use of the product mid-summer in a citrus grove in the San Joaquin Valley, there could be substantial conversion of the active ingredient to a highly toxic degradation product in the duff under trees under actual field conditions which would be hazardous to field workers.

The CDFA review may include:

1. Determining the use pattern (geographic, season, equipment-type etc.) of the proposed product;
2. Determining significant possible human exposure hazards;
3. Evaluating the adequacy of use instructions and/or regulations that are in place to inform users of the possible use hazards and how to avoid excess exposure.
4. Evaluating the adequacy of information provided to recognize illness due to exposure if it occurs;
5. Determining the adequacy of first aid information; and,
6. Examining the availability of data to support medical management.

Data from the toxicology base, plus those from the additional health and safety studies that are sometimes required, allow for the estimation and calculation of potential exposure hazards. For some products, experience already gained allows for a quick determination that adherence to the proposed or existing use instructions should result in a low hazard use situation. On the other hand, a number of the pesticides considered for registration have significant hazards from either a short-term or long-term exposure standpoint. These hazards are estimated and/or calculated to determine if a favorable recommendation on the proposed registration can be given, and if not, whether additional restrictions would be expected to acceptably reduce the hazards of use.

For example, a particular product might be a highly dusty wettable powder with only moderate acute toxicity but with demonstrated potential for producing chronic effects. The calculations for the hazard evaluation are based upon the total workday measurement of the skin and inhalation exposure to this pesticide when it is used in accord with the label instructions. This potential daily dose is then adjusted by the estimated 24-hour dermal

absorption rate. This final figure is compared to animal test data for the dose expected to produce a specific adverse effect. The safety factor for this specific effect will then be calculated to determine if it is adequate to protect the workers. In some cases, exposure assessment might not give an acceptable safety factor for a mixer/loader; but, if this product were repackaged in water-soluble packets or if it were reformulated to be used as a liquid product and then required to be transferred through a closed system, the hazard might be acceptably reduced.

Of particular concern are potential adverse effects such as carcinogenicity and those which are developmental (primarily those which occur prior to birth). The following is given to illustrate the assessment process by CDFA of these two types of adverse health effects.

Cancer Risk Assessment

Based on chronic animal bioassay and mutagenicity testing results, a review is conducted in accord with EPA guidelines using a total weight of evidence review including use of the appropriate mathematical model to determine whether the chemical is a significant animal carcinogen. If positive results are confirmed, the chemical undergoes further evaluation. Human epidemiology data, if available, is also reviewed and evaluated. Positive human data take precedence over animal data.

From worker exposure data, an average and a maximum exposure level for each type of work activity involved with pesticide use is calculated. The total yearly body dose is derived from the daily exposure and the number of days of exposure per year in performing the job. Residue levels (including degradation products) found in treated crops or food product are used to assess consumer risk.

Developmental Toxicity

The CDFA follows EPA's toxicology procedures for evaluating teratogenicity. A number of vital parameters are considered in this ranking of teratogens. These include, but are not limited to, the nature of major and minor malformations and lethality, at which dosages morphological changes of the fetuses are being observed, dose range, maximum no observable effect level (NOEL), and the route of administration.

The animal NOEL (mg/kg/day) divided by the maximum total body dose (mg/kg/day) estimated to be absorbed by the worker during one typical workday represents the safety factor that is obtained for that particular work activity. This is then compared to the acceptable safety factor. From this, it is determined whether adequate safety is reasonably achievable. In such cases when there is an insufficient safety factor, additional mitigation measures are taken to ensure adequate worker protection if registration is to be granted or maintained.

Embryotoxicity and other adverse reproductive effects receive somewhat different evaluations.

Safety Factors

The following is CDFA's current guideline for safety factors required to mitigate various toxicological effects. If the desired safety factor cannot be achieved, use of that product is not authorized or continued unless additional practices to increase safety can be applied such as use of closed system transfer, water-soluble packaging, specifying less hazardous work practices, or requiring special protective clothing and equipment.

For each of the following adverse effects, a minimum safety factor is applied to the NOEL in test animals. In animal exposure studies for example, the maximum dose level which produces no detectable clinical illnesses, no biochemical changes, no histopathological changes and no deaths is considered to be the NOEL.

<u>ADVERSE EFFECTS</u>	<u>USUAL MINIMUM SAFETY FACTOR</u>
1. Acute Effects	
a. Cholinesterase inhibition	10 fold
b. Other acute effects	20 fold
2. Effects on Reproduction	
a. General reproduction (including reductions in (1) number of off-spring, (2) fertility, (3) sperm counts, and (4) size of testes, etc.)	50 fold
b. Embryotoxic/fetotoxic effects	50 fold
c. Teratogenic effects	50 to 300 fold
3. Delayed-Onset Neurotoxic Effects	50 fold
4. Non-Oncogenic chronic effects	50 fold
5. Oncogenicity including mutagenicity	

The lifetime risk of cancer is usually first calculated by using one of three mathematical models: (1) the one-hit model, (2) the multi-stage model, and, (3) a choice of a third model usually the Weibel model or the improved Mantel-Bryan model. The risk calculations are made by relating the dose response curve obtained from animal exposures to the human exposure estimates. A total weight of evidence review is conducted and the use of statistical modeling data alone is avoided. Guidelines used in decision-making follow:

<u>Exposed Group</u>	<u>Acceptable Risk</u>
a. For consumers of treated crops	Not more than one additional estimated case of cancer in the lifetime of 1,000,000 exposed persons.
b. For farm field workers	Not more than one additional estimated case of cancer in the lifetime of 300,000 exposed persons.
c. For mixers, loaders, applicators	Not more than one additional estimated case of cancer in the lifetime of 100,000 exposed persons. For a few

years, a risk as high as 1 in 10,000 may be tolerated in the case of extreme need.

Adequacy Of Mitigation Measures

After all relevant data are fully evaluated, an assessment is made as to the adequacy of the possible mitigation measures to protect workers from hazards of use. The label with its use instructions may be accepted and the product may be registered without further concern. On the other hand, one or more of the following conditions may be required before the product is considered for registration by the CDFA: (1) the EPA may be advised of the desirability of requiring a label change giving more specific use instructions, or the registrant may recognize the need to ask EPA for such a label change; (2) a California regulation on the use may be enacted (which will have the same effect as a label change, but this can take several months to accomplish); (3) the product may be made a California restricted or regulated material which will allow imposition of specific permit requirements or regulations (this process can also take a number of months); (4) closed system transfer of liquid pesticides may be required, (this is currently required for all toxicity Category I liquids, when specified on labels regardless of the toxicity category and when specifically required by regulations); (5) change in the product's formulation may be required to reduce excess hazards (e.g., reduce dustiness); (6) water-soluble packaging of the more toxic powders may be required; (7) minimum field reentry intervals may be set by regulation (a several-month process unless they are adequately specified on the label); (8) medical supervision may be required by regulation; and/or (9) detailed safety training may be required for specific pesticides.

EXAMPLE OF VALUE OF BIOLOGIC MONITORING DATA

The current usually-employed methods for measuring worker exposure to pesticides involves measurement of residues in the breathing zone and/or on the skin and then by using dermal absorption rate data collected in rodents or monkeys, to calculate probable human exposure. For several reasons this often overestimates exposures. Below we have summarized our recent study of captan exposures of strawberry harvest workers, to illustrate this point.

Introduction: Studies of the dermal pesticide exposures of strawberry harvesters have been reported by Pependorf et al. (4), Everhart and Holt (5), Zweig et al. (6), Winterlin et al. (7) and Ritcey et al. (8). Some of the data accumulated from studies of strawberry harvesters figured prominently in the development of the empirical transfer coefficient (commonly called the Zweig-Pependorf factor) of 5000 cm²/h which can be used to relate dislodgeable foliar pesticide residues to hourly dermal pesticide exposures of fieldworkers (Zweig et al. (9)). The transfer coefficient seems to be a helpful tool to provide a first estimate of the dermal exposure of fieldworkers engaged in work tasks such as harvesting fruits and vegetables or picking flowers in a greenhouse.

We developed three estimates of strawberry harvester exposure to captan based upon dislodgeable foliar residues, dermal dosimetry, and

biological monitoring. We were particularly interested in the quantitative relationship between the estimates due to their critical importance in the risk assessment process. Additionally, we sought to measure the degree of mitigation of the captan exposure provided by the use of chemically-resistant gloves.

METHODS

Setting

In June 1987, we obtained the cooperation of the California Strawberry Advisory Board and Mr. Larry Galpers of Telles, Incorporated, Watsonville, California. The Board provided financial support to compensate the producer for any lost time and productivity when we stopped work to put on measurement devices or to collect samples. Telles, Incorporated gave us complete access to a 72 acre strawberry farm which was considered by all concerned to be representative of the approximately 16,000 acres of California strawberry production.

The strawberry beds were planted with 18,500 plants/acre of the Pajaro and Selva varieties. The plants were grown on elevated beds (14") with 52" centers. The plants were well past their peak production, e.g. 10-12 crates per row at peak versus 2-3 crates in July. This provided maximal seasonal worker contact with treated foliage. Production data were recorded (crate = 10 pounds).

Two crews of workers (approximately 35-50 workers/crew) pick the fields twice in each 6-day week (8 hour days) of the picking season which extends from April to October. The crews consisted of men and women in apparent good health (85 percent were below age 35) with up to a maximum of 20 years experience as strawberry pickers. They usually wear long pants and long-sleeved shirts to protect themselves from the generally cool weather of the area where strawberries grow well. Some of the men wear short-sleeved shirts, and others roll up their sleeves as the mornings warm. Women additionally wear scarves which cover most of their face. All of the women and less than 5 percent of the men normally wear chemically resistant gloves to protect their hands from dirt and strawberry juice.

For this study, a crew of 40 male volunteers was assembled by the foreman and the ranch manager. Males were selected to provide sufficient numbers of workers of one sex to meet experimental objectives. Additionally, because men did not usually wear gloves they permitted establishment of glove/no glove groups without reducing any worker's normal protection. The gloves were 13", chemically resistant, and made from Long Service[™] rubber. The assistance provided by the foreman was critical to obtaining the enthusiastic cooperation of the pickers. Throughout the study, the ranch management served as an effective liaison between CDFA staff and the fieldworkers.

Captan Application

Four days before harvest, each part of the field was treated with Captan 50 WP (4 lbs. a.i./acre) tank mixed with Benlate 50 WP (1 lb

a.i./acre) and Vendex (2 lbs. a.i./acre). Two hundred gallons of spray mix were applied to each acre using a fixed-boom sprayer. Samples of tank mix were collected for captan and tetrahydrophthalimide (THPI) analysis.

Foliage Monitoring

Prior to the captan application and during each day of the study, foliage samples were collected. Each sample consisted of forty 2.54 cm diameter leaf discs (Birkestrand punch) replicated three times before and after harvest. Samples were taken along a diagonal line from 10 rows of strawberries in a given section of the field. Eleven sections of the field were sampled. The sample jars were sealed with aluminum foil, capped, and kept on wet ice until they were transported to the laboratory for captan residue analysis.

Dermal Dosimetry

Measurements of dermal exposure and evaluation of the protection provided by gloves were made on days 2 and 3 of the study. In order to have minimal effects on normal work practices and to assure that CDFA staff could adequately assist each workers, the crew was randomly divided into two groups of 20. On a given day each group of 20 was provided with a set of 100% cotton, tight fitting long underwear to be worn beneath normal workclothes. Each worker was given the underwear the day before their scheduled monitoring. The group was further divided into "glove" and "no glove" subgroups.

Dermal exposure was monitored during a 4-hour, morning work period. The workers carefully removed the dosimeters in temporary change rooms constructed in the back of two rental trucks using sheets and plastic pipe. The garments were placed into Zip-lock^R bags and stored on dry ice until processing. At that time an arm sample and a leg sample were prepared, iced, and transported to the laboratory.

Concurrently, handwashes were done on each subject using 400 ml of 1% Surten solution contained in a one gallon Zip-lock^R bag. Each person washed their hands for two one-minute periods. Handwashes (800 ml) were subsampled (500 ml) and stored on dry ice until transported to the laboratory.

Urine

Pickers were provided three or four polyethylene urine collection bottles each day. The bottles were held in insulated boxes in the field during the work day and two unused bottles were taken home each night. Creatinine levels were measured in each 24-hour void at a local clinical laboratory as an indicator of compliance.

Extraction, Cleanup and Analysis

Dislodgeable captan residues on leaf samples were prepared according to Gunther et al. (10). Samples were shaken three times with Surten solution and extracted three times with ethyl acetate after addition of Na₂SO₄. After volume reduction the samples were analyzed by gas chromatography.

Captan was analyzed on the dermal dosimeters in a similar fashion. The initial extract was prepared by separately tumbling individual sets of underwear arms and legs with ethyl acetate.

Urinary THPI (cis-1,2-dicarboximido-4-cyclohexene) was determined as reported by Winterlin et al. (7). Twenty-five ml aliquots were extracted with methylene chloride, filtered, dried, and taken up in benzene. The extract was analyzed using Hewlett-Packard 5880A gas chromatograph with a N/P ionization detector. The minimum detectable level of THPI in urine was 0.03 ug/ml and recoveries ranged from 80 to 89 percent.

Subsequently a set of 10 of these urine samples were further analyzed by Morse Laboratory, Sacramento, CA. A pH II clean-up and nitrogen specific electrolytic conductivity detector were used to achieve a minimum 0.005 ppm sensitivity. At 0.02 and 0.01 ppm sensitivity the recoveries of THPI were 75 and 67 percent respectively.

Statistics

The difference between mean (3 replicates) pre- and post-harvest dislodgeable foliage residues were compared using paired t-tests. A randomized block design was used to investigate potential mitigating effects of gloves on dermal captan exposure. Factors included in the linear model for analysis included glove assignment, day, and a glove interacting with day term. If no glove assignment by day interaction was determined (P<0.10), then we made comparisons for the two remaining effects. All analyses were made using Type III Sums of Squares in the SAS General Linear Model Procedure.

Since the exposure data were skewed, the variable itself, a natural logarithmic transformation, and rank transformed data were analyzed.

RESULTS

Production

The 40-man crew picked 12, 12.2, and 11 acres of strawberries on the three days of the study (Table 1). The number of crates picked was 916, 1413, and 1239, respectively. The work period was approximately seven hours each day. The high yield of strawberries on day two was made up of 832 crates of Selvas and 581 crates of Pajaros.

It was the subjective observation of the foreman and ranch manager that the use of gloves slowed some pickers on the first day of the study.

They reported normal picking rates for the following two days of the study. They additionally noted that after the study had ended only a few of the men continued to wear their gloves.

Dislodgeable Residues

Eleven separate large beds of the ranch were sampled for pre- and post-harvest dislodgeable captan residues. The pre-harvest sample mean \pm S.D. was 2.4 ± 0.6 ug/cm², and the post-harvest mean was 2.1 ± 0.5 ug/cm². These measurements provided direct evidence that the spray mix was uniformly applied to the areas under study. Additionally, the post-harvest samples contained 0.3 ug/cm² less dislodgeable residue (P=0.024) as evidence of the substantial contact by the picking crew.

Dermal

Dermal Dosimetry and Handwashes

Fieldworkers were carefully observed. Prior to our selecting cotton long underwear as a whole body dosimeter; we had monitored only hands, arms, and legs since those were the body parts that had substantial contact with treated foliage. A similar strategy was used by Ritcey et al. (8) who assessed exposure using oversleeves and leggings. Table 2 shows exposure data for days two and three of the study. Gloves very effectively reduced hand exposure as indicated by the captan and THPI in the handwash. Approximately 50 percent of the captan was recovered as THPI in the handwashes. No other samples contained more than trace amounts of THPI. As expected due to limited worker contact during picking, low amounts (<15 percent) of captan exposure were the result of leg contact. Since the gloves covered more than half of the forearm, the apparent mitigating effect of gloves may be overestimated to a small extent by the simple calculation of percent of total captan recovered on the arm dosimeter.

Urinalysis

Captan is rapidly absorbed through the skin (2 percent of applied dose per hour) and urine is the primary route of excretion. These factors contribute to the feasibility of using biological monitoring to gauge captan exposure.

There are numerous metabolic studies of the fate of captan in rats, but unfortunately none are available for humans. ¹⁴C-Carbonyl has been used to study the THPI moiety of captan by Hoffman et al. (11). When ¹⁴C-captan was orally administered, 85 percent of the radioactivity was recovered in urine within 96 hours. The metabolic scheme includes hydrolytic cleavage of captan to yield THPI. Subsequently four additional metabolites are produced by hydroxylation, epoxidation, hydrolysis, and hydroxylation-rearrangement. Human exposures were estimated assuming that THPI was a captan metabolite, and that it constituted 15 percent of the urinary metabolites which were 85 percent of the dose.

The samples analyzed by electrolytic conductivity were 72 hour composites and they were estimated to contain about 200 ug captan equivalents (48 percent absorption; 15/85 metabolism). The actual values are shown in Table 4. The median was 0.005 ppm and the range was <0.005 to 0.014 ppm.

Estimates of Exposure

Estimates of fieldworker exposure based upon dislodgeable foliar residues, dermal dosimetry, and biological monitoring differ markedly. From the 2.4 ug/cm² dislodgeable residue level on foliage, a daily dermal exposure of 96 mg/day was calculated (5000 cm²/h; 8 h). Based upon dermal absorption studies in the rat, the absorbed dose (24 h) was assumed to be 48 percent (2%/h; 24 h) resulting in an effective dose of 46 mg/captan/day. Based upon the rat metabolic work, 84 percent of an oral dose of captan would be eliminated in 24 hours and 15 percent of that would be the metabolite, THPI. If anything, larger amounts of THPI in urine might be expected following dermal exposure since the metabolic (especially hydrolysis) contribution of gastrointestinal tract would be minimized (or totally eliminated) following dermal exposure. As a result, daily urine would be expected to contain about 3 mg THPI or 2.5 ppm THPI. This level of THPI is approximately 500-times the minimum detectable level (0.005 ppm). Apparently, the approach of using the dislodgeable residue and the rat dermal absorption rate data for estimating dermal captan exposure is of limited usefulness since it predicts much higher exposure than occurs based upon urinalysis of the workers. Due to the lack of specific human absorption and metabolic data and our poor understanding of the foliage-worker transfer process, the basis for the overestimate can not be identified at this time.

Dermal dosimetry also apparently estimates dermal captan exposure. Following careful observation of strawberry pickers, we measured arm, leg, and hand exposures using tight-fitting, long underwear to capture captan which contacted the extremities. Handwashes were analyzed to estimate hand exposure. Workers without gloves had three to four times greater exposure than gloved workers. In Table 2 gloved worker exposure is assumed to be 10 mg captan/day and the potential THPI exposure 0.3 mg THPI/day. The captan exposure was about one-ninth of that estimated using dislodgeable residues. The hypothetical level of THPI was approximately 60-times the minimum detectable limit. Both dislodgeable residue and dermal dosimeter based exposures are apparent overestimates under the assumptions given in the preceding paragraph.

DISCUSSION

This study demonstrates the magnitude of fieldworker exposure generated using dislodgeable foliar residues, dermal dosimetry, and urine monitoring. The quantitative differences are striking and would ultimately result in substantially different risk assessments and mitigation measures. The dislodgeable foliar residue approach gives investigators an estimate of exposure, but it probably should be made

more work task specific to reflect major differences in foliage contact between strawberry pickers and lettuce cutters on one hand and peach thinners and grape pickers on the other. At this time we are trying to retrospectively construct a set of transfer coefficients to represent high, medium, and low contact work tasks. The possible influence of the physical and chemical nature of the deposit of the applied pesticide will also be considered. Furthermore, additional data will be gathered in a long term evaluation of the regulatory usefulness of the transfer coefficient to estimate dermal exposure.

In the specific example presented here the apparent transfer coefficient was 250-675 cm²/h for gloved fieldworkers as compared to the generic 5000 cm²/h coefficient (9). Gloves and long sleeved shirts may be necessary to maintain low fieldworker exposures in crops containing high (>0.5 ug/cm²) dislodgeable foliage residues. This is especially important for chemicals such as captan that have significant chronic toxicity and potentially long periods of exposure.

In a more general vein, it seems that biological monitoring holds promise of providing more direct estimates of pesticide exposure. That potential is currently severely limited by inadequate absorption and metabolism data. This problem will not disappear, and exposures continue. Procedures to index worker exposures using key metabolites may have to be developed rather than complete pharmacokinetic data packages for each active ingredient if accurate exposure assessments are to be obtained. The index would include an established range of exposures for a particular work task and would require an understanding of factors affecting the excretion of key urinary metabolites. This is not a call for experimental pesticide disposition studies in humans. Instead it is acknowledgment of a growing need for better human data and a reminder that sensitive and specific analytical procedures used to measure vanishingly small amounts of chemical residue on treated crops can be adapted to the trace analysis of pesticide metabolites in urine. Fieldworkers, producers, registrants, regulators, and the general public will benefit from the significantly more reliable assessments of risk which will result.

The dermal exposure estimate based upon data developed from metabolic and dermal absorption rate studies in rats and the dislodgeable residue measurements on the strawberry plants is more than two orders of magnitude greater than estimates derived from the analysis of urine. As a result the apparent cancer risk will be dramatically reduced by the urinary metabolite procedure.

TABLE 1

WATSONVILLE STRAWBERRY FIELDWORKER STUDY

<u>DATE</u>	<u>DAY</u>	<u>ACRES</u>	<u>CRATES</u>	<u>STRAWBERRY</u>
7/20	1	12	916	PAJARO
7/21	2	12.2	1413	SELVA; PAJARO (832) (581)
7/22	3	11	1239	PAJARO

TABLE 2

DERMAL CAPTAN EXPOSURE OF STRAWBERRY PICKERS (MILLIGRAMS)

<u>DAY 2</u>	<u>ARMS</u>	<u>LEGS</u>	<u>HANDWASH</u>	<u>TOTAL</u>
NO GLOVES	9.2	1.2	11.4	21.8
GLOVES	3.6	0.7	0.3	4.6

<u>DAY 3</u>	<u>ARMS</u>	<u>LEGS</u>	<u>HANDWASH</u>	<u>TOTAL</u>
NO GLOVES	27.4	0.8	14.4	42.6
GLOVES	10.9	1.3	0.2	12.4

TABLE 3

RANGE OF DERMAL CAPTAN EXPOSURES OF STRAWBERRY PICKERS (MILLIGRAMS)

Estimates

<u>DAY 2</u>	<u>MEAN</u>	<u>±STD</u>	<u>MEDIAN</u>	<u>MINIMUM</u>	<u>MAXIMUM</u>
NO GLOVES	22	6	22	10	30
GLOVES	5	5	3	1	17

<u>DAY 3</u>	<u>MEAN</u>	<u>±STD</u>	<u>MEDIAN</u>	<u>MINIMUM</u>	<u>MAXIMUM</u>
NO GLOVES	42	32	31	17	117
GLOVES	13	10	10	1	29

TABLE 4

TETRAHYDROPHthalimide IN THREE-DAY COMPOSITE URINE SAMPLES

<u>FIELDWORKER</u>	<u>THPI (PPM)</u>
1	0.006
2	0.005
3	<0.005
4	<0.005
5	0.005
6	0.010
7	<0.005
8	0.014
9	ND
10	0.005

MLD = 0.005 PPM

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