FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

A Set of Scientific Issues Being Considered by the Agency in Connection with DDVP (Dichlorvos) Risk Issues

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency in connection with DDVP (Dichlorvos) Risk Issues. The review was conducted in an open meeting held in Arlington, Virginia, on July 30, 1998. The meeting was chaired by Dr. Ernest E. McConnell (ToxPath, Inc.). Other Panel Members present were: Dr. Janice Chambers (Mississippi State University); Dr. Rory Conolly (Chemical Industry Institute of Toxicology-CIIT); Dr. Michael Cunningham (National Institute of Environmental Health Sciences-NIEHS); Dr. Amira Eldefrawi (University of Maryland School of Medicine); Dr. Richard Fenske (University of Washington); Dr. David Gaylor (National Center for Toxicological Research); Dr. Charles Hobbs (Lovelace Respiratory Research Institute); Dr. Gordon Hard (American Health Foundation); Dr. Ronald J. Kendall (The Institute of Environmental and Human Health, Texas Tech University/Texas Tech University Health Sciences Center); Dr. Ross Leidy (North Carolina State University); Dr. Genevieve M. Matanoski (The Johns Hopkins University); Dr. Fumio Matsumura (University of California); Dr. Herbert Needleman (University of Pittsburgh); Dr. Christopher Portier (National Institute of Environmental Health Sciences-NIEHS); Dr. J. Routt Reigart (Medical University of South Carolina); Dr. Mary Anna Thrall (Colorado State University); and Dr. John Wargo (Yale University).

Public Notice of the meeting was published in the Federal Register on June 19, 1998.

Oral statements were received from the following:

Robert Becker, MD, representing SRA International, Inc.

Dr. Bruce Bernard (SRA International, Inc.)

Dr. David Brusick (Covance)

Dr. Samuel Cohen (University of Nebraska), representing SRA International, Inc.

Dr. Jay Goodman (Michigan State University), representing SRA International, Inc.

Dr. Stephen Harris (Stephen B. Harris Group)

Mr. Bill Harvack (Amvac Corporation)

Dr. Judy MacGregor (Toxicology Consulting Services)

Dr. Rudy Richardson (University of Michigan), representing SRA International, Inc.

Dr. Jay Schreider (California Department of Pesticide Regulation)

Dr. David Wallinga (National Resources Defense Council)

Dr. Susan Youngen (Novigen Sciences)

Written statements were received from the following:

SRA International

General Comments from SAP Members

The Panel reviewed a considerable amount of material related to Dichlorvos (DDVP), including the PD 2/3 (Special Review Action, Notice of Intent to Cancel) issued by the Agency in September, 1995. Agency response to public comments received on the PD 2/3 was completed in June, 1996. In the PD2/3, the Agency proposed cancellation of DDVP uses for: (1) residences (including pet flea collars, total release foggers, pressurized aerosols, crack and crevice treatment); (2) tobacco warehouses; (3) ornamental lawns; (4) turf and plants; (5) commercial, institutional and industrial areas; (6) commercial vehicles (airplanes, trucks, shipholds and rail cars); (7) warehouses; (8) bulk, packaged, or bagged nonperishable processed and raw foods and; (9) hand-held application in mushroom houses, greenhouses and passenger buses.

The July 8, 1998, DDVP Risk Assessment Issues paper prepared by the Agency stated that since these events, the registrant had voluntarily cancelled uses in tobacco warehouses and in commercial transportation vehicles. The Panel inquired as to what actions, if any, the Agency has taken in regard to the other uses for which cancellation was proposed. It appears that the Agency has continued its analysis of toxicity and exposure data for DDVP during this time, but has not proceeded with any regulatory actions. It was not clear that such reanalyses have changed significantly the risk assessments which underlay the PD 2/3 document. The Panel urged the Agency to clarify remaining risk assessment issues for DDVP and to move forward, where appropriate, with proposed regulatory actions.

The Panel recognized the substantial number of public comments at this session. Scientists representing the registrant presented the results of an independent advisory panel's deliberations on the genotoxicity and carcinogenicity of DDVP, as well as the use of cholinesterase inhibition data in the regulatory process. These presentations in turn raised questions regarding neurotoxicity testing for DDVP. The Panel is providing the following comments and concerns on these topics.

<u>Genotoxicity Comments:</u>

The Panel noted that the registrant has submitted data from a series of mechanistic studies in an attempt to demonstrate that dichlorvos is a nongenotoxic agent similar to butylated hydroxyanisole (BHA) and not a genotoxic agent like 1-methyl-3-nitro-1-nitrosoguanidine

(MNNG). The studies attempted to prove that dichlorvos induces replicative DNA synthesis (RDS) and cell proliferation and does not induce unscheduled DNA synthesis (UDS) indicative of DNA damage. The experimental design of these studies is unvalidated and flawed. Mice were administered a single dose of dichlorvos, BHA or MNNG or vehicle control by gavage. Animals were serially sacrificed up to 48 hours later. Forestomachs were removed for histopathological examination or incubated with 3H-thymidine in vitro for assessment of UDS or RDS. These data cannot be evaluated for several reasons. Single dose studies have little relationship to the longer term toxicity of a chemical. Acute effects seldom predict chronic effects. In the present experimental design, any UDS in the forestomach induced by dichlorvos would be masked by the RDS, since the RDS measurement evaluates an entire nucleus darkened by 3H-thymidine and UDS evaluates small dots of radioactivity incorporated into the nucleus. Simultaneous measurements are not compatible. Additionally, *in vitro* administration of the label is not reliable and has not been validated as has *in vivo* administration of the label.

A parallel study measured 3H-thymidine incorporation/mg DNA. This is an outdated technique that provides meaningless data without information about the subcellular location of the label or the cell types involved.

Overall, the UDS assay has been shown to be quite insensitive to mutagenic chemicals with the exception of potent alkylating agents. A positive response is a clear indication of DNA damage, but a negative does not indicate nongenotoxicity.

The Panel noted that mutagenic batteries were developed in order to provide a rapid and inexpensive screen to determine the potential of a chemical to induce cancer. They are generally simple tests with a narrow response. These data from these tests are generally reproducible in that a chemical positive in one test is generally positive in other similar tests. There is a fairly poor concordance (both positive and negative predictivity) for the results of chronic bioassays such as those conducted by the NIH National Toxicology Program (NTP). The best test to date is the Ames test, which has about 65 percent concordance. This includes almost 20 percent of chemicals judged positive in the Ames test that result in negative rodent cancer results. These "false positives" (or genotoxic noncarcinogens) result not from a failure of the *in vitro* test but from the complexity of the carcinogenesis process in the whole animal. These processes in the intact animal that are not reflected in mutation assays include absorption, disposition, metabolism and elimination (ADME) considerations, cytotoxicity resulting in compensatory hyperplasia, mitogenesis, metabolic enzyme induction or inhibition, etc.

Therefore, the results from whole animal bioassays supersede the results of *in vitro* tests. Compounds that are inactive in mutation tests but cause cancer in the whole animal are considered nonmutagenic and carcinogenic and generally are regulated as carcinogens in the U.S. Similarly, compounds that are positive in mutation tests but do not cause cancer in the whole animal should be regulated as noncarcinogens.

Carcinogenicity Comments:

Several Panel members commented on the carcinogenicity of dichlorvos. There is an emerging view based on cumulative experience by some toxicologic pathologists that mononuclear cell leukemia in the Fischer rat may be a unique type of cancer and not induced *de novo* by compound administration. In the case of DDVP, both low and high doses showed a doubling of mononuclear cell leukemia (MCL) incidence without a clear dose-response relationship and only a tenuous link with respect to carcinogenic potential. Concerning the mouse forestomach tumors, DDVP joins a group of compounds that can cause irritation and/or breakdown of the physiological gastric mucosal barrier and, indirectly, forestomach tumors through sustained cytotoxicity and cell regeneration. Thus, quantification of the cancer risk assessment of this compound should be a nonlinear threshold approach based on the forestomach tumors. The negative cancer ingestion bioassay in rats contributes to the weight-of-evidence evaluation of the carcinogenic potential of DDVP. In particular, this study reduces the likelihood that the rat leukemia seen in the corn oil gavage study is due to a directly genotoxic mechanism of DDVP. Such an effect is not expected to show a route-of-administration effect.

There is compelling evidence to disregard MCL in the Fischer rat. MCL is one of the most common background tumor types in this strain, and has been referred to as Fischer rat leukemia. Other rat strains and mice do not develop MCL, and there is no human correlate to this disease. Additionally, chemically-related increases in MCL exhibit advanced severity grades for this lesion in treated rats compared to controls. Analysis of the MCL in the DDVP gavage study showed no significant increase in severity of the MCL with increasing dose, indicating that these lesions are background. Overall, the high background and variability in the incidence of this tumor, as well as its species and strain specificity, make it an invalid response for human risk assessment. However, it should be noted as in the case of benzene carcinogenicity, early studies showed carcinogenicity in Zymbal's gland in rats for which there is also no human correlate.

Forestomach carcinogenesis in oral gavage bioassays in the absence of glandular stomach or any other target organ carcinogenesis is likely due to the chronic irritancy, inflammation, and cytotoxicity during chronic bolus dosing, resulting in extraordinarily high local concentration of the chemical. This chronic toxicity to the forestomach puts cells into chronic mitosis and provides an environment for heightened sensitivity to food-borne carcinogens endogenous in diets or to the likelihood of promotion of naturally occurring, spontaneous background tumor cells being stimulated to divide. In addition, the forestomach in rodents acts as a storage site where irritant chemicals in the food have prolonged contact with the sensitive squamous epithelium lining, a situation that does not pertain to humans. Thus, the feeding study of DDVP, which did not induce tumors in the forestomach or any organ, should be taken into consideration.

One Panel member noted that in assessing the overall carcinogenicity of DDVP, the Agency should be careful of overly simplistic interpretation of p-values. The fact that the leukemia p-value for the female rats does not achieve statistical significance is not of as great an interest as the fact that the marginal finding ($p=0.07$) in females supports the significant finding in males. In addition, the marginal finding in the Japanese study is also in the same direction as that seen in the males from the NTP study, but for a different route for which absorption could be remarkably different.

In conclusion, the weight of the evidence suggests carcinogenicity in animals treated with DDVP with a non-linear dose-response. However, the compound is considered a weak carcinogen acting via a secondary or indirect mechanism.

Cholinesterase Inhibition Comments:

The Panel noted that because of the vital role played by acetylcholine (ACh), acetylcholinesterase (AChE) exists in several-fold excess at cholinergic synapses and a great deal more in the blood, presumably to protect the body against this highly bioactive molecule. The various cholinesterase isozymes differ in their response to organophosphates. Plasma cholinesterase is usually more sensitive than red blood cell acetylcholinesterase. The least sensitive is usually AChE, which is located in cholinergic synapses (in muscles, glands, and brain), and in some cases the degree of its inhibition correlates best with toxicity symptoms. The blood enzymes act as reservoirs for removing organophosphates from circulation, thus reducing their concentrations at the critical targets. These are the cardiac, smooth and skeletal neuromuscular and neuroglandular acetylcholinesterases. However, Panel members differed on whether inhibition at these targets correlates best with the toxicity symptoms. A Panel member commented that there are limited data on inhibition of peripheral cholinesterase.

No-observable-adverse-effect-level (NOAEL) or lowest-observable-adverse-effect-level (LOAEL) values, based on inhibition of plasma or blood cholinesterases, do not necessarily reflect toxicity and may in some cases give higher values, which is in fact less conservative. In terms of acute studies, Panel members provided different opinions on the best approach for measurement of acetylcholinesterase inhibition. One Panel member commented that the best approach to measure inhibition of acetylcholinesterase is in cardiac, skeletal, smooth muscles or brain. However, another Panel member remarked that the methodology is problematic for measuring acetylcholinesterase inhibition in cardiac, skeletal, or smooth muscles. Thus, consideration of acetylcholinesterase inhibition in cardiac, skeletal, or smooth muscles would be premature at this time. In terms of subchronic and chronic studies, development of tolerance should also be considered. While data support the idea that high levels of brain cholinesterase inhibition are required to elicit clinical signs of toxicity, 60 percent brain cholinesterase inhibition is too great to consider as a threshold for adverse effects.

It is important for the Agency to adopt consistent use of the terms NOEL and NOAEL with its documents and decisions.

Neurotoxicity Testing Comments:

In the discussion of cholinesterase inhibition, the Panel raised concerns regarding the suggestion that clinical signs should serve as an indication of adverse effects compared to more subtle behavioral modifications, which should be considered appropriate for judging toxic responses. In 1996, the SAP recommended that the Agency develop validated test protocols for Scheduled Analysis of Operant Behavior (SCOB) studies to be used to test neurotoxins. A guideline for the SCOB is available. This type of testing, or any behavioral data used to determine the toxicant's neurotoxicity, has not been conducted for DDVP.

One Panel member noted that these methods are not new entries into the study of pesticides. In 1975, Mertens et al. used SCOB to study responses in a number of species exposed to mevinphos, and McMillan studied the effects of parathion on scheduled responses. Carbamates have been examined using SCOB, as have pyrethroids. It cannot be said that reliable neurotoxicity data have been obtained if the methods to evaluate these data are old and insensitive. Thus, one Panel member concluded that in the absence of reliable neurotoxicity data, retaining the FQPA 10x Safety Factor should be obligatory. Another Panel member noted that it is critical that the Agency formulate a policy of what will be required for neurotoxicity testing. More discussion on retaining the FQPA 10x Safety Factor for DDVP is provided below in response to question one.

On a generic note, the Panel advised the Agency to carefully consider the nature of the tests used for operant behavior to test cognitive function, which may be used a part of regulatory guideline studies. Many such tests require food deprivation in order to provide motivation for the animals to seek a food reward. The reduced weights and reduced levels of body fat in these animals are likely to provide less depot storage sites for lipophilic xenobiotics, such as the case for many pesticides, and therefore the pharmacokinetics of the compounds would be altered. This altered pharmacokinetics, in turn, would change the bioavailability of the compounds and therefore alter the tissue doses of the compounds. Such confounders could alter the degree of effect and the interpretation of the data.

Questions to the Scientific Advisory Panel

The Agency posed the following questions to the SAP regarding DDVP (Dichlorvos) Risk Issues.

1. Application of FQPA Safety Factor

The standard Subdivision F Guideline developmental and reproductive toxicity studies submitted to the Agency showed no indication of increased susceptibility of rats, mice, or rabbits to in utero and/or postnatal exposure to dichlorvos. However, based on experimental results reported in the open literature, the OPP HED Hazard Identification Assessment Review Committee has requested a prenatal developmental toxicity study in guinea pigs to assess the findings reported in the open literature concerning the effect (decreased brain weight) of dichlorvos on the developing guinea pig brain. While there are no data gaps with respect to the standard Subdivision F Guideline requirements, these guideline requirements do not require measurement of fetal or neonatal brain weight.

An FQPA safety factor of 3x has been recommended for the acute and chronic dietary risk assessments, and to the residential exposure assessment for the general population including infants and children primarily due to uncertainties surrounding the results described in the literature study.

(A) Can the Panel comment on the appropriateness of using guinea pigs as a representative test species for assessing the likelihood of chemical-induced developmental effects in

humans?

The Panel noted numerous technical limitations in the Mehl et al. guinea pig study. If more information is obtained from the Mehl et al. authors, an additional point to be determined is the amount of variability, or lack thereof, in brain weights within a single litter. This study is essentially an N=1 study since the 3 or 4 pups in most of the doses were from a single dam. This type of inter-litter variability is critical in interpreting this study.

The suggestion to repeat the guinea pig brain weight study using an acceptable protocol has merit, but it raises the issue of whether or not a study judged to be seriously deficient should be used to justify additional research, given the adequacy of the data in species well established for the evaluation of reproductive and developmental toxicity. Further, if a scientifically rigorous guinea pig study is conducted, there will not be a body of historical data to provide a context for evaluation of the new data. The importance of historical context was clearly illustrated in the discussion of the male F344 rat leukemia, where the high historical control incidence of this tumor type was an important factor in evaluating the significance of the dichlorvos-induced tumors.

The Panel concluded that flaws in the Mehl et al. study limit its significance and do not permit the Agency to reach any conclusions regarding developmental toxicity. However, the study suggests the possibility of a developmental effect on the brain---despite its flaws---and the Panel believes that the Agency should further investigate the following:

* If the study were conducted according to an acceptable experimental design, would the effects be replicated?

* Is the guinea pig an acceptable test species to predict the risk of human developmental effects?

The Agency's obligation to explore these issues is especially important given the mandate of the FQPA to ensure protection of infants and children from significant risk.

(B) In view of the above, does the Panel consider it appropriate to retain an FQPA safety factor? If so, of what magnitude (i.e., 3x or 10x)?

Introduction

The Panel's consideration of an appropriate safety factor for DDVP led to a more general discussion about the basis for such a factor. The Panel noted that the FQPA is clear and categorical on the use of the 10x safety factor for children. The FQPA states that the factor shall be employed, and that a different margin of safety may be used only if, on the basis of reliable data, such margins "will be safe for children." This is a declarative and dispositive statement. The Panel noted that pesticide registrants -- and the Agency -- face a clear burden of proof of safety to justify relief from the 10x safety factor. The standard of proof, in terms of data sufficiency and reliability, is a high hurdle. The decision to relieve the 10x safety factor should be made by the Agency only when it has determined that both toxicity and exposure data are sufficient and reliable to provide an accurate estimate of risk. A discussion of DDVP toxicity and exposure data

in relation to retaining the FQPA 10x safety factor is provided below.

Toxicity Issues Concerning 10x

The Agency stated during this session that the current required toxicity database for dichlorvos does not suggest that developing systems -- in utero or juvenile -- are more sensitive than adults. In fact, the results of the rabbit developmental study, which showed a lack of developmental toxicity even at maternally lethal doses, suggest that even at maternally lethal doses, the developing fetus may be more resistant to DDVP than adults. The Agency asked the Panel to consider a recent study in guinea pigs which showed diminished brain weight. As noted above, the Panel felt that one could not reach any conclusion about developmental toxicity with this study. The Panel also noted the absence of any developmental neurotoxicity studies and reiterated the importance of exploring effects on higher brain functions (e.g., cognition, memory, and learning) that may result from lower doses than those affecting brain weight. The use of an alternative margin of safety requires that tests of toxicity be sensitive enough to find relatively subtle brain effects. These tests have not been used for DDVP, so a declaration of safety is unwarranted at present.

Lipid-soluble neurologic drugs that also do not require bioactivition, such as DDVP, are absorbed via inhalation more efficiently and reach the brain faster and in higher concentration than the oral route. Absorption through the GI is via the portal circulation where it is exposed to liver esterases that hydrolyze and detoxify it, thereby reducing it in the blood level. On the other hand, DDVP absorbed through the lungs goes to the brain prior to the liver. Thus, the route of exposure is very relevant to its toxicity.

Exposure Issues Concerning 10x

The Panel heard extensive public comments demonstrating that little is known about human exposure to DDVP following residential applications. The Panel also raised several questions concerning DDVP exposure. First, studies to determine chemical transport and fate following residential or exterior applications that could result in interior contamination have not been conducted. Second, the Agency had not conducted analyses that demonstrate how exposure is likely to accumulate across media. Third, no systematic monitoring of drinking water has been conducted. In the absence of these data, it is not possible to determine if significant additional exposures are occurring from water ingestion and associated dermal and inhalation exposures. In addition, the definition of the term "residential" was unclear and could presumably extend to schools, commercial establishments, and other institutional settings.

The Panel concluded that aggregate exposure assessments need to be conducted for compounds such as DDVP for all scenarios in which infants and children are likely to be exposed. Such aggregate exposures should identify all plausible sources and exposure pathways for children and indicate the completeness and reliability of data for each pathway. If data gaps are identified through this process, these should be noted explicitly in the Agency's review, with discussion as to how the Agency plans to address the uncertainty such gaps represent. The quality of such aggregate exposure assessments must be considered in deliberations regarding retention or

modification of the FQPA 10X safety factor.

The Panel concluded that cumulative exposure needs to be considered in deliberations regarding retention or modification of the FQPA 10X safety factor. The child serves as the integrator of exposure to multiple compounds which have a common mechanism of action. In the case of organophosphorus pesticides such as DDVP, for example, the Agency's discussions should be informed by an awareness of the full spectrum of residential uses of these compounds and the potential for children's exposures. It is difficult to understand how consideration of children's exposure to pesticides on a case-by-case basis, without an understanding of cumulative exposures, can provide the foundation for an informed FQPA 10X safety factor decision.

Conclusion

The Panel noted that considerable uncertainty remains concerning developmental neurotoxicity and probable patterns of human exposure. After thorough discussion, the SAP was divided as to whether the FQPA safety factor should be 10x or reduced to 3x, as proposed by the Agency. Those that supported retaining the 10x safety factor did so because of insufficient data on developmental neurotoxicity and human exposure. However, other Panel members supported reducing the FQPA safety factor to 3x, concluding that the totality of the developmental toxicity data suggest that the developing fetus is no more sensitive to DDVP than adults, although human exposure data were insufficient to reduce the safety factor to 1x. Several Panel members expressed concerns that the Agency 10x decision memorandum for DDVP did not include exposure uncertainty factors.

2. Resin Strip Residential Exposure Scenarios

Estimates of residential post-application inhalation exposure from use of dichlorvos-impregnated resin strips have been calculated in several ways. Air monitoring data from a published literature study have been used to permit comparison among the following approaches:

1) time weighted average for chronic exposures;

2) percentile of time spent in proximity of resin strips;

3) time weighted average for descriptors of various heating, ventilation, air conditioning (HVAC);

4) an indoor air Multi-Chamber Concentration and Exposure Model (MCCEM);

Does the Panel have any preference(s) among the above approaches? If so, why?

The Agency has proposed four methods for estimating inhalation doses from residential use of DDVP resin strips and has asked the Panel to evaluate these methods. The Agency's question provoked a more general discussion of residential exposure. Two major points emerged from this discussion. First, it was unclear to the Panel why the Agency has continued to develop

new methods for estimating doses after issuance of the PD 2/3 and a response to public comments. The PD 2/3 stated that the "Agency is proposing cancellation of all products registered for residential uses . .. EPA has determined that the Margin of Exposure (MOEs) are significantly less than 100 for all methods of application in the home and for post-application exposure to residents." (p. 50369). The MOE for DDVP resin strips was determined to be 20. This finding was reaffirmed in the June 4, 1996, Response to Public Comments on the DDVP PD 2/3. The Agency should more clearly articulate a rationale for continued analysis of exposure in light of these previous decisions.

Second, the Panel expressed concern that the Agency's current exposure assessment for DDVP resin strips (and perhaps for indoor residential exposures in general) fails to address the multi-route nature of residential exposure. The four exposure models consider only exposure by inhalation, and therefore neglect to consider DDVP concentrations in rugs, upholstery, or clothing which may lead to dermal exposure and/or oral exposure (i.e. hand to mouth activities). All of these are known to be sinks for organic molecules, and the behavior of toddlers, ignored in all models, makes these data of critical importance. Children of this age spend large amounts of time crawling over carpets, and putting their hands in their mouths. None of the models include such sources and pathways, and so suffer from a substantial specification error. One Panel member recounted recent research findings which have shown that residues of dichlorvos in soil vacuumed from carpet increased some 70 times over a 5 to 6 month period (ca. 0.01 ppm, 14 days; 0.7 ppm, 150 days) following an outdoor perimeter application. The formulation used was a combination of chlorpyrifos/dichlorvos. How much of this residue was transferred either to the skin or from hand to mouth contact is unknown, but one can assume that some gets into the body. Data including soil, surface and airborne residues should be included in any exposure model. In summary, the data on which the Agency's current residential exposure assessment for DDVP resin strips is based must be considered incomplete. The registrant should be requested to furnish this information to allow an informed estimate of exposure to be made.

In answer to the Agency's methodological question, the DDVP resin strips under review are time release products; i.e., DDVP vapor is emitted from the strip over time. Current products (e.g., AMVAC Insect Strip ®) contain from 1.7 - 16.6 grams of DDVP active ingredient and are designed to release this material for a time period of up to 4 months. Label information can be used to calculate treatment rates ranging from 11-35 mg DDVP per cubic foot.

All of the exposure analyses presented in the Agency documents rely on data generated in a 1973 study of 15 homes using Shell No-Pest ® Insecticide Strip (Collines and DeVries, 1973). The study was designed to measure DDVP residues in air and food under "practical use conditions". The treatment rates in that study for the areas sampled were 3 - 28 mg DDVP per cubic foot. Thus, the products used in the 1973 study do appear to be representative of current products, although the treatment rate range of the earlier product was lower than that of current products.

The Panel believes that a time-weighted average approach is most appropriate for estimating inhalation doses for residents exposed to DDVP resin strips, since the health concern is chronic exposure of residents to DDVP. Previous residential studies have shown that pesticides

will remain indoors for prolonged periods due to the "protective" effects of the interior of structures. One can take indoor air, or other residue data, and determine exposure at any point of time after application. A time-weighted average can be determined based on actual data and factored into what ever equation is used to determine exposure. The indoor air model (MCCEM) holds potential for producing more sophisticated analyses of exposure, but does not improve estimates derived from the time-weighted average approach in this case. The "percentile of time spent" method seriously underestimates residential exposures, since it does not account for ambient exposure throughout most of the day. Each of the methods used by the Agency are discussed in detail below.

Method I. Time weighted average for chronic exposures

The time-weighted average (TWA) calculated by the Agency in 1987 contains errors which do not appear to have been addressed in subsequent documents. The calculation mistakenly treats the 1973 data as "ppm" rather than µg/L, as stated in the article. The original data have been transformed to mg/m^3, apparently because of the assumption that they were ppm. The resulting values are about an order of magnitude greater than they should be (i.e., µg/L and mg/m^3 are equivalent units). Furthermore, the method used to calculate a TWA is incorrect. For example, the Day 7 value was used to represent Days 2-7; instead, the average of Days 1 and 7 should be used to represent concentrations for Days 2-6.

Method II. Percentile of time spent in proximity of resin strips

This calculation relies on self-reported time spent on activities from the National Human Activity Pattern Survey (NHAPS). It is unlikely that the values generated in this survey have been validated. The values selected for this analysis were times that "consumers spent in activities working with or near pesticides, including bug sprays or bug strips". The use of short intervals when respondents were actively handling or in close proximity to insect strips should be included in the calculation of exposure for these individuals, but such activities do not seem relevant to the children who live in the residence. This approach makes the tacit assumption that if one is not "working with or near" the strips, then exposure is zero. This would seem to be contradicted by the data reported in the 1973 study, as well as by more general knowledge of gas and vapor distribution within residential environments. One cannot make the assumption that airborne residues of dichlorvos will remain only in the vicinity of the strips. These airborne residues will move readily and will be found in measurable quantities in air in all rooms of a house. This approach seriously underestimates residential exposure to DDVP from resin strips and should not be pursued.

Method III. time weighted average for descriptors of various heating, ventilation, air conditioning (HVAC)

This approach is referred to as Method III in the July 8 DDVP Risk Issues paper and is described in detail in the June 29 Agency memo on MCCEM. This analysis is confined to Day 1 inhalation exposure and so is not a time-weighted average analysis. It uses a single exposure duration value for all cases, in contrast to Method II, which used different percentiles from

NHAPS data to determine exposure duration. It also relies on the 1973 study data. The 1973 study selected homes in three categories related to presumed differences in ventilation, but no measurements of HVAC systems or air exchange rates were made. The differences across the three categories seem negligible for the purposes of the analysis at hand. This approach could prove useful for more complex data sets but seems unnecessary in this case.

Method IV. Indoor Multi-Chamber Concentration and Exposure Model (MCCEM)

This approach employs a model developed recently for the Agency. The model uses source emission rates to predict environmental concentration over time. It is not clear that use of a constant emission rate from the 1973 study is appropriate for this application. The air concentration data indicate that the emission rate is not constant. It is likely that the manufacturer has excellent data on emission rates of these products, since such data are the basis for efficacy claims. The model does not appear to accurately reflect the values measured in the study from which it draws its data. This model may prove useful with a more complete database. It is not known if the model has been validated for DDVP.

The Panel noted that none of the models take into account the factors affecting pesticide movement indoors. The environmental conditions (e.g., temperature, relative humidity) that an individual maintains will vary from house to house. In addition, the way a house is kept (i.e., cleaning frequency), traffic patterns, the presence of children and pets all impact on pesticide movement and concentration. It may prove impossible to collect reliable data on all such factors affecting residential exposures, but Agency assessments should address these concerns and consider the uncertainty associated with them in any exposure models or calculations. The Panel reiterated its support of the use of the Agency's Standard Operating Procedures (SOPs) for residential exposures. The SOPs were reviewed by the Panel at its September, 1997 meeting.

An additional issue raised in the discussion of DDVP resin strips related to the relevance of real world exposures for risk management. The central point is whether Agency exposure analyses should be bounded by label requirements, or whether they should incorporate knowledge of real world exposure conditions. The specific issue involved the appropriate duration of a time-weighted average (TWA) calculation for residential exposure. Agency analyses of the Collines and DeVries data presented to the Panel included a one day (Day 1) dose estimate, a 56 day analysis using the MCCE Model, and a 91 day TWA calculation. The product label recommends replacement of pest strips after 120 days. A public comment during the meeting by the DDVP registrant indicated that the TWA should be calculated for this time interval. Other label instructions which might be construed as boundaries for exposure analysis include no use of resin strips in homes with infants, no use in children's bedrooms, and no use in food preparation or consumption areas. The Panel believes it is reasonable and important to consider whether a consumer who has just purchased a product to rid a residence of insects will necessarily comply with all of these restrictions. If not, then the Agency needs to determine how to ensure protection for residential occupants, particularly for infants and children.

The notion that exposure analyses must be bound by label requirements rather than real world exposures may have originated in studies of occupational pesticide exposure. In the case of

restricted use pesticides, for example, sales are restricted to vendors who are aware of their potential hazards, and the compounds can be applied only by individuals who have been certified as applicators (or those who work under the direct supervision of a certified applicator). The ability to read and understand the label is tested, and continuing education and periodic recertification are required. Also, the Agency has the ability to enforce adherence to label requirements and apply meaningful penalties (e.g., loss of certification). The actual practice has its problems, but the point here is that the regulatory system is designed to control use practices.

Residential exposures, however, differ in nearly all respects from the pesticide applicator example: products such as resin strips are sold "over the counter" and are widely available; sales people are unlikely to be knowledgeable about risks; consumers exhibit great variability in literacy, command of the English language, and predispositions to read or follow label instructions. Monitoring of residential uses is not conducted by federal or state agencies, nor apparently by the registrant, and regulatory agencies are extremely reluctant to enforce label requirements in private residences.

The Panel believes that better knowledge of real world use practices would serve to improve residential exposure analyses, and that the lack of knowledge about actual use (and misuse) for such consumer products as resin strips is an important area of uncertainty in residential exposure analysis. The Panel encourages the Agency and registrants to consider collecting such data to improve estimates of residential exposures.

One final issue raised by the Panel concerned the use of toxicological data to interpret exposure estimates. In regard to use of the value of 0.05 mg/kg as the NOAEL for chronic inhalation, the derivation of this value from the 1974 chronic inhalation study in Carworth Farm Strain E rats is not documented in the EPA material. Such documentation should be provided as part of its analysis. Apparently the percentage of absorption of DDVP following inhalation is not known for either rats or people. This represents a weakness in the data and is further reason not to use route- to- route extrapolation. During discussions, some mention was made of studies in pigs that indicate absorption of 20 percent of DDVP following inhalation. If such studies are available, they should be reviewed by the Agency. Care needs to be taken to ensure data values are consistent and conclusions are correct and transparent. For example, the NOAEL for inhalation is stated to be 0.5 ug/L in Table 2 of the Agency's background document. In fact, it should be 0.05 ug/L. In addition, many of the MOE's in the June 12, 1998, Agency memo of Jaquith to Scheltema (Table 1) appear to be incorrect. Some of the MOE's on page 37 of the memo are also incorrect.

FOR THE CHAIRPERSON:

Certified as an accurate report of findings:

Paul I. Lewis

Designated Federal Official

FIFRA/Scientific Advisory Panel

DATE:_____