

**Workshop**

**"Exposure of Children to Pesticides"**

Berlin, September 27<sup>th</sup> to 29<sup>th</sup>

**Abstracts**



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## **Children Versus Adults: Differences and Similarities in Response to Environmental Pollutants and Chemical/Drug Poisons**

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### **Objective:**

Minimal published data are available to evaluate quantitatively risk of exposure and response of infants and children to environmental pollutants and some chemical/drug poisons. Biologic differences in infants and children compared to adults allow possible prediction in some cases of potentially increased or potentially decreased toxicity risks to some environmental chemicals.

### **Results:**

These biologic/physiologic differences include:

- as much as a 2.7 fold greater skin surface area:body mass ratio,
- proportionally larger brain size,
- rapid brain growth, greater cerebral blood flow per unit mass of brain weight, developmental changes in brain neurotransmitters,
- a 40-fold to 60-fold greater lung respiratory minute ventilation rate per square meter of lung surfact area,
- decreased but later increased (compared to adults) liver hydroxylation,
- glucuronidation and other metabolism, developmental ontogeny of cytochrome P450 isozymes,
- decreased renal glomerular filtration and tubular secretion,
- protein binding to albumin/alpha-1-acid glycoprotein and chemical tissue binding,
- and increased intracellular glutathione

Known examples from the available limited database will be discussed including hexachlorophene and benzyl alcohol brain stem cell necrosis, lead (Pb) poisoning, acrodynia, acetaminophen hepatotoxicity, chloramphenicol gray-bab syndrome, gentamicin nephrotoxicity and ototoxicity, dystonic adverse drug reactions, nitrate-induced methemoglobinemia, fetal alcohol syndrome, retinoid embryopathy, neural tube birth defects, breast milk environmental pollutant exposure, ozone air pollution, passive cigarette smoke exposure, and environmental endocrine disruptors.

### **Conclusion:**

All of these differences have potential implications for toxicological risk for infants and children, in some cases greater risk and in some cases lesser risk than adults.

## Impact of Pharmacogenetics for Toxicity of Xenobiotics in Children

*M. Schwab, Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany*

Interindividual variability in xenobiotic metabolism and in part in drug transport is extensive and is one of the major determinants for the toxicity of xenobiotics. The causes for this variation are of genetic, physiological, pathophysiological and environmental origin. The influence of the genetic background on toxicity of xenobiotics is particularly interesting considering that the reasons and mechanisms frequently are still unclear. Pharmacogenetics seek to identify genetic factors that contribute to interpatient and interdrug variation in toxicity to xenobiotics. With the completion of the Human Genome project and identification of new genes, the next tasks are to understand the influence of genetic factors on susceptibility of xenobiotics and to apply genetic profiling.

‘Pharmacogenetics’ is the study of variability in drug response due to heredity. This includes inherited differences in metabolism, disposition and transport of xenobiotics as well as in drug sensitivity (drug targets such as receptors) [figure 1]. The term pharmacogenomics emphasizes the development of novel agents based on newly discovered genes. Variations from a predominant allele are often referred to as genetic polymorphisms, a term which is used to describe variants occurring with a frequency of 1% or greater in a human population. The significance of a polymorphism depends on the phenotype to establish its functionality. The majority of pharmacogenetic differences that have so far been characterized on a molecular basis represents variability in xenobiotic-metabolizing enzymes. Most of the remaining appear to represent alterations in receptor affinity, transporters, or protein binding. For example, pharmacogenetic differences can be striking (up to 10000-fold) whereas differences in binding are generally less than 20-fold.

Genetically determined variability in the level of expression or function of these enzymes has a profound effect on toxicity and efficacy. Individuals can be classified by phenotyping as either poor-, extensive- or sometimes as ultra-rapid metaboliser. By means of molecular genetics allelic variants (e.g., mutation, deletion, amplification) can be detected which can affect protein function in comparison to wild-type. Poor metabolisers are carriers of inactivating mutations, which result in a complete lack of active enzyme and for example a severely compromised ability to metabolise xenobiotics. On the other side polymorphisms not only affect metabolic elimination but can also be important in the conversion of prodrugs to their active form. There is good evidence for some drug classes that polymorphic expression of metabolizing enzymes (e.g., NAT 2, CYP450 2A6, 2C9, 2C19, 2D6, TPMT, UGT1A1) is responsible for either therapy failure, exaggerated drug response or serious toxicity after taking the „standard and safe“ dose of drugs. The CYP450s are a multigene family of enzymes found predominately in the liver that are responsible for metabolic elimination of most of the xenobiotics currently used in medicine. For example, CYP2D6 is possibly the most popular CYP450 polymorphism and numerous studies on molecular mechanisms and genotype-phenotype relationship have been performed. Figure 2 summarize exemplarily the functional consequences of the CYP2D6 polymorphism.

Whereas ethnic and racial diversity in the frequency of polymorphisms of xenobiotic-metabolizing enzymes are studied extensively, limited data are available concerning the expression of xenobiotic-metabolizing enzymes during human development and ontogeny. Additionally, information about the biochemical or physiological factors that modulate up-regulation and down-regulation of enzyme activity during development is also incomplete. Interindividual variability in drug metabolism in preterms, infants, toddlers and older children is the result of a complex interaction between pharmacogenetics, development, and additionally exogenous factors (e.g. disease, nutrition). Both pharmacogenetic and developmental

factors affecting the activity of xenobiotic-metabolizing enzymes should be taken into account for better understanding of toxicity of xenobiotics in children.

Figure 1.

**Current research areas in Pharmacogenetics.** Pharmacogenetics currently comprises the study of polymorphic xenobiotic-metabolizing enzymes and drug transporters and drug targets such as drug receptors.

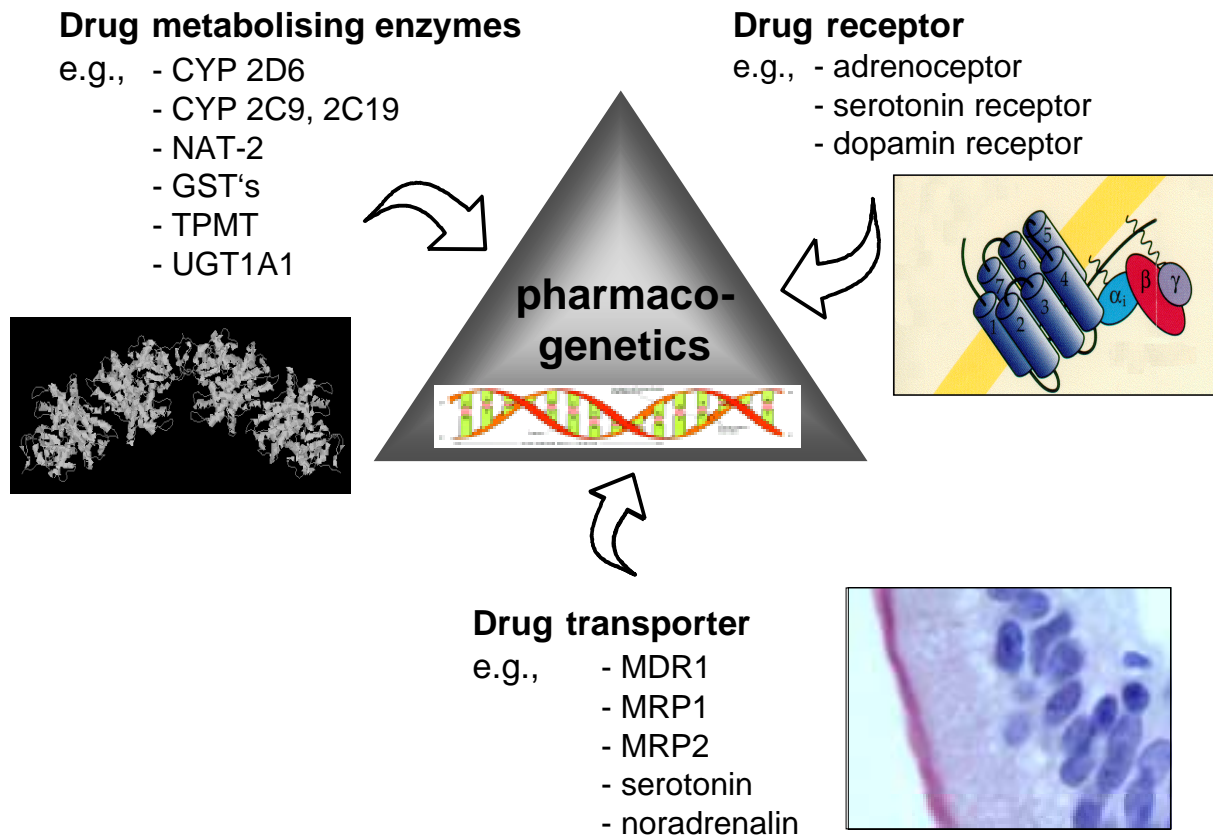
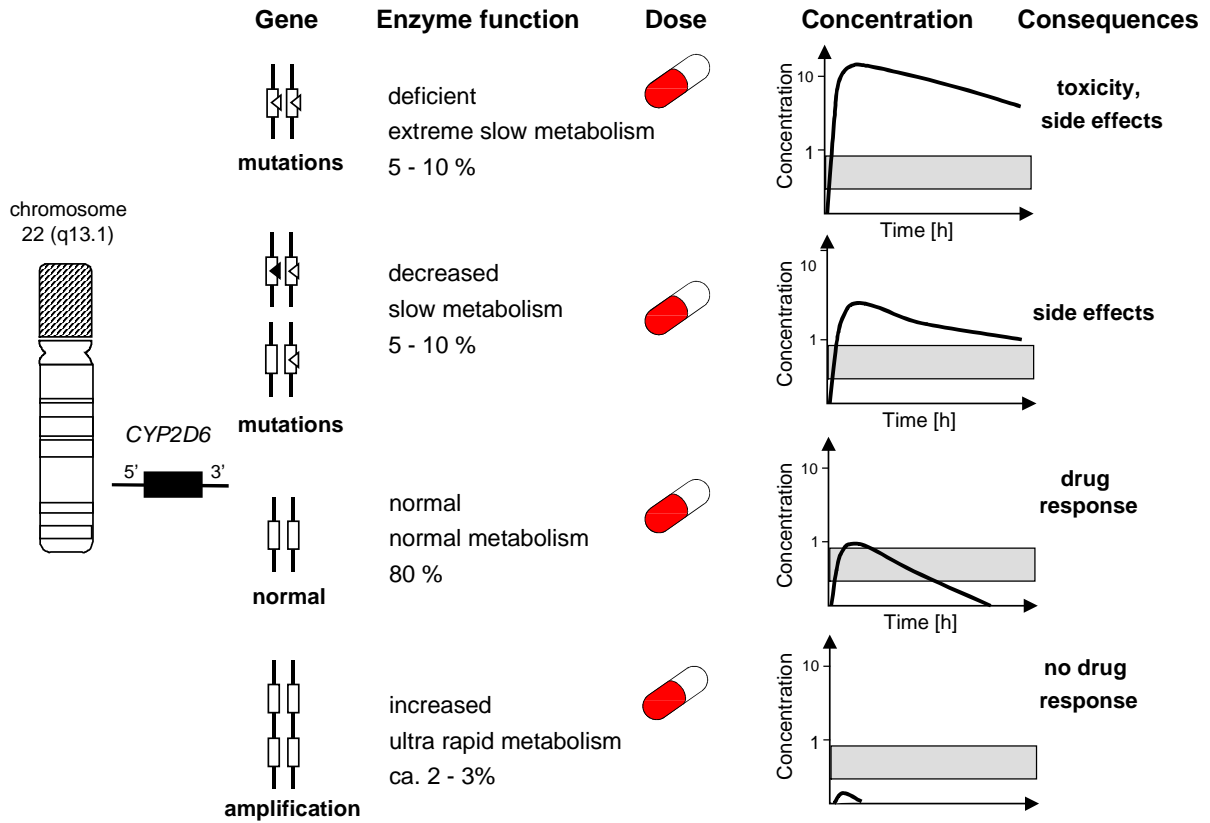


Figure 2

**The genetic polymorphism of CYP2D6 (debrisoquine/sparteine-polymorphism) and its consequences for drug therapy.** Patients who receive the same standard dosage of a CYP2D6 substrate show marked differences in drug plasma concentrations according to their constitutive CYP2D6 genotype and consequently may be at increased risk for either drug toxicity (poor metabolizer) or therapeutic failure (ultra rapid metabolizer).



## **A Review of the Effects of Low-level Exposure to OP Pesticides in Children**

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### **Abstract**

In 1999 the UK Government made an announcement confirming that the Ministry of Agriculture, Fisheries and Food, the Health and Safety Executive, and the Department of Health (DH) would develop a targeted research programme to take forward research recommendations from the DH's Committee on Toxicity and UK regulatory committees. The main focus of these recommendations was that research to address the possibility of long-term adverse neurological or neuropsychiatric health effects following exposure to low doses (doses that do not cause signs or symptoms of acute toxicity) of organophosphate pesticides was required. In response, a workshop was convened to assist in determining the scientific input and approaches required to meet identified research needs\*. One of the issues arising from the workshop discussions was that possible susceptible groups, including children exposed directly or in the womb, should be included in future research.

Consequently, the MRC Institute for Environment and Health is currently undertaking a detailed critical review of the scientific literature relating to the possible adverse effects of foetal and childhood exposure to low-levels of OPs. The review aims to cover both the effects of OPs in general and also the specific effects of particular OPs to which the foetus and children may be exposed in the UK. The specific methods and objectives of the review are detailed below.

### **LITERATURE SEARCH.**

Following discussions with the sponsor and external contractors a detailed search of all major medical, toxicological and environmental on-line databases has been conducted in order that relevant reference material be identified. References obtained will, where possible, be supplemented with additional material identified from expert knowledge, professional contacts, and the 'grey' literature. The search strategies used will be recorded and included in the final report.

### **AN ASSESSMENT OF THE EXPOSURE OF FOETUSES AND INFANTS TO OPs.**

Although the remit of the project does not include a detailed exposure assessment, exposure to OPs, for example via the mother, and through the diet, will be included, in order to put the potential health effects into context. The influence of amateur use of OPs in homes and gardens, exposure from agricultural or occupational use, and from medicinal and veterinary products will be considered. The review will primarily focus on sources of exposure considered likely in the UK.

### **IDENTIFICATION OF POTENTIAL ADVERSE EFFECTS.**

The available evidence for adverse health outcomes (with particular reference to neurotoxic, developmental, immunotoxic, behavioural and cancer effects) from low-level exposure to OPs is being evaluated. Human findings (which are limited) are being supplemented by findings from studies on animals and will be interpreted in the light of a review of the potential biological mechanisms of OP induced toxicity. Particular attention is being given to the specific developmental nature of the foetus and child, and whether this could influence the toxicity and/or health end-points. The review will also seek to identify potential critical windows of susceptibility during which a child or foetus could be particularly vulnerable to exposure to OPs.

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\*Copies of workshop proceedings available at: [www.doh.gov.uk/opwksshop.htm](http://www.doh.gov.uk/opwksshop.htm)

## **AN ASSESSMENT OF THE PLAUSIBILITY THAT THE POTENTIAL EFFECTS ARE CAUSALLY ASSOCIATED WITH EXPOSURE.**

The review will include an assessment of the quality of the toxicological and epidemiological data presented, the plausibility that the effects are causally linked to the exposure, and relevance of the data to children in the UK. Areas of uncertainty will also be highlighted.

## **A RISK CHARACTERISATION OF THE POTENTIAL HEALTH EFFECTS OF OPs IN CHILDREN.**

The likelihood of health effects arising from OP exposure levels in the UK will be undertaken by analysing the exposure data and estimating total daily intake where possible, for best and worst case scenarios, for both foetus and child. Once the (potential) exposure has been established, the levels at which health effects occur will be assessed and the risk of health effects occurring from these exposure levels evaluated. An attempt will also be made to evaluate the risks to health occurring later in life as a result of foetal or childhood exposure.

## **DATA GAPS AND RECOMMENDATIONS.**

The review will provide recommendations for further research based on identifying gaps in current knowledge and particular areas of uncertainty.

## **Modeling Exposures to Pesticides: Approaches and Modeling Needs**

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Estimation of exposures of children to pesticides requires careful consideration of sources and concentrations of pesticides that may be present in different environmental media and in foods and beverages consumed by children, as well as the different routes and pathways of exposures specific to daily activities of children of different ages. In recent years a number of (aggregate) exposure models has been developed by various researchers to account for exposures to a single chemical from different routes and pathways. Cumulative exposure models, dealing with aggregate exposures to more than one chemical are, however, still mostly in the developmental stage. The EPA's Office of Research and Development (ORD), National Exposure Research Laboratory (NERL) has developed a probabilistic model (Stochastic Human Exposure and Dose Simulation Model, or SHEDS) that predicts the range and distribution of aggregate personal exposures and doses within a population as well as the uncertainty in the model estimates. The model framework is being developed with an initial case study for the pesticide chlorpyrifos and the population of young children. At the present, the SHEDS model includes the inhalation and dietary ingestion routes in addition to dermal contact and non-dietary ingestion. The model can simulate an individual's exposure up to a year time frame, accounting for multiple pesticide applications in the residential environment, in addition to single day estimates for different post-application time periods. In addition, a user-friendly interface has been developed for the aggregate SHEDS-Pesticides model with both exposure researchers and regulators in mind as potential users. Future versions of the SHEDS model will include more complete characterization of pesticide dose and metabolite concentrations in the body by coupling SHEDS to NERL's Exposure Related Dose Estimating Model (ERDEM). SHEDS and other aggregate or cumulative pesticide exposure models need rigorous evaluation and independent verification against carefully designed field studies. All of the models suffer from limitations of available input information on critical exposure factors for infants and young children, especially dermal and non-dietary transfer efficiencies or coefficients by activity type, location, surface and contact characteristics. In general, models need to demonstrate, by sensitivity analysis, which inputs or parameters are of special concern for future revisions. This information will in turn assist the design of future field exposure and biomonitoring studies that will then generate the critical data necessary for refining the existing pesticide exposure models. In order to develop more robust models with more complete input data, repeated or longitudinal pesticide concentration measurements, time-activity data, and frequency of pesticide usage information in homes, day care centers and schools are also needed. Finally, the form of model outputs that are most useful to regulatory and scientific agencies and the public also needs to be identified.

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## Requirements for Models Used for Exposure Assessment to Pesticides

*Leah Rosenheck, Greensboro, NC:*

The passage of the Food Quality Protection Act (FQPA) in 1996 focused pesticide risk assessments toward understanding the potential exposure of children to dietary, drinking water, and non-dietary residues of pesticides.

Initial efforts by the North American agrochemical industry to address these risk assessments included the formation of task forces dedicated to developing exposure data to children and adults resulting from the use of pesticides in residential settings. The Outdoor Residential Exposure Task Force (ORETF), while not formed to specifically address FQPA, has conducted numerous exposure, user survey, and children's activity studies specific to the outdoor uses of pesticides on lawns, gardens, ornamentals, and trees. The Non-dietary Exposure Task Force (NDETF) is conducting exposure studies for the indoor applicator and post-application use of pesticides. The REJV (Residential Exposure Joint Venture) is a smaller consortium of industry members whose goal is to gather a statistically representative temporal survey data on consumer pesticide use, both inside and outside the home. These data will identify and provide information regarding all pesticide chemicals used in and around the home, including demographic information for the households involved in the survey, and concurrent use patterns (use of two or more products during toxicologically relevant time periods), which are critical for conducting both aggregate and cumulative risk assessments. The Farm Family Exposure Study (FFES) is a joint effort by a number of agrochemical companies to determine the exposure received by farmers, their spouses, and children through biological monitoring of urine. The FFES effort is complimenting the Agricultural Health Study (AHS) being conducted by the U.S. EPA and other federal agencies.

Concurrent with the development of exposure and usage data necessary for the assessment of children's exposure to pesticides is a joint effort by the US Environmental Protection Agency and Industry to assess potential modeling tools to estimate the aggregate and cumulative exposure of adults and children to pesticides. Models that are currently under evaluation in North America are the SHEDS model developed by EPA's Office of Research and Development, Calendex developed by Novigen Sciences, Inc., CARES/RExY developed by Infoscintific.com under contract to the industry, and Lifeline developed by Linea under a cooperative agreement with the US EPA's Office of Pesticide Programs. The effort involves a cooperative exercise by EPA, Industry, and the model developers aimed at determining how each model handles the relatively robust data collected so far by the task forces in each model and understanding the output from each model.

Biological monitoring of children's exposures to pesticides is essential to providing a frame of reference of actual absorbed dose potential in which to compare the model outputs. Efforts to this end are also underway. The US EPA is conducting research in the area of children's exposure to environmental contaminants. NERL has initiated a 3-year pilot program of monitoring preschool children in North Carolina and Ohio. Samples of indoor and outdoor air, dust, soil, urine, and hand wipes will be collected as will samples of food and beverage consumed by the children and their care-givers. The Minnesota Children's Pesticide Exposure Study has recently released the analysis of urinary metabolite levels from a 102 children sample. In addition, individual agrochemical companies are conducting biological monitoring studies to determine the absorbed dose to specific pesticides following their use in residences.

Based on the efforts to date in North America the following conclusions regarding model requirements can be reached:

- The models require extensive exposure databases to permit probabilistic assessment of dermal and inhalation exposure
- Use information is critical to the models. Such information must include detailed knowledge of activity patterns and pesticide use patterns including use of the same pesticide at multiple sites and the use of different pesticides and their temporal relationship
- As the major contributions to exposure such as direct contact with treated surfaces or application are quantified with robust data that replaced initial exposure assumption the exposure assumptions regarding less significant potential sources of exposure that can also be difficult to uniquely quantify such as dust, object to mouth contact, or by indirect emissions begin to drive the model's output
- The aggregate and cumulative models have become very complex and will require validation against population exposure and absorbed dose monitoring.
- Emphasis should be given to biological monitoring of children's exposure to develop an understanding of the range of exposures children receive
- The models developed as reliable predictive tools must be based on a firm understanding of children's actual exposure potential.

## Exposure of Children to Creosote from Wood Impregnation on Playgrounds

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Creosote (coal tar) is a complex mixture of high-boiling compounds which arise during the distillation of coal. Main constituents of creosote are polycyclic aromatic hydrocarbons. Some of these, e.g. benzo[a]pyrene, dibenz[a,h]anthracene are supposed to be carcinogenic. In general, benzo[a]pyrene (BaP) is used as a marker substance for PAH mixtures. According to EU Directive 94/60/EC creosote with a content of 50 – 500 mg BaP/kg may not be sold to the private consumer but can be used in industrial processes, some national Directives within the EU are even more restrictive. Creosote is widely used as an impregnation agent for wood applied outdoors such as garden fences, tadpoles, railway sleepers etc. As wooden outdoor playing devices (e.g. sandbox edgings) are also impregnated with creosote children may come in contact with it. The following routes of exposure are possible: contact with freshly impregnated wood (dermal), exudation of creosote components from the wood surface of pressure impregnated wood such as railway sleepers which were in the past often used as edgings on playgrounds (dermal), leaching into the surrounding soil (dermal and oral), or contact with contaminated dust or evaporation into air (inhalation). Oral uptake of contaminated soil is especially relevant for small children having extensive hand-to-mouth transfer.

The dermal, oral and inhalation exposure of playing children to the BaP content of impregnated wood was estimated with the following assumptions: regular stay on playgrounds of 3- to 8-year old children, frequency about 100 times/year, exposure time 4 h each, maximum BaP content of creosote 50 mg/kg. From these calculations it can be concluded that three routes of exposure are most relevant: the dermal exposure to contaminated sand or soil in the vicinity of the impregnated wood, the dermal exposure from freshly impregnated wood and the oral exposure via contaminated soil. For these routes doses in the order of magnitude of 0.1 to 0.5 ng/kg bw x d were estimated. The inhalation exposure via contaminated dust appears to be lower by a factor of about 10. Inhalation of evaporated BaP can be neglected as due to the low vapour pressure gaseous BaP is not to be expected in the ambient air. Exudation of manually impregnated wood can be also neglected as surface applied creosote weathers completely within one or two years. The possible dose from exudation processes is hardly calculable at all as it depends on weather conditions.

These estimations contain a number of plausibility considerations concerning personal habits of playing children. This leads to a highly uncertain risk assessment concerning carcinogenic effects. The compilation of reliable data on playing habits and anthropometric parameters (e.g. body weight, skin surface of children) combined with probabilistic methods is therefore of special interest also with regard to cumulative risk assessment.

## Homes with wool carpets, treated with permethrin – Exposure of adults and children

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Wool carpets and textile floor coverings with wool yarn are usually treated by pyrethroid insecticides (mainly permethrin) to protect against damage by moths and creatine-digesting beetles.

It is known, that permethrin has a low mammalian toxicity. Nevertheless, an increasing number of health complaints after indoor use of pyrethroids and in connection with permethrin-protected wool carpets have been reported by the Federal Institute for Consumer Health and Veterinary Medicine (BgVV). Up to the end of 1998 about 348 of such suspected cases (39 cases in connection with wool carpets) were recorded.

The controversial discussion after indoor exposure to permethrin prompted the BMBF and the IVA to initiate and sponsor this present study.

In order to identify a possible impact of permethrin in wool carpets in homes on their inhabitants, indoor monitoring in 80 homes and biological monitoring of their 145 inhabitants (including 31 children < 14 years) were carried out.

During a 2-year period, the house dust was collected once and the suspended particles twice. These samples and carpet fibers were analyzed for permethrin. Where possible, two urine samples (collected over 24 hours, or spontaneous urine from crawling children) were collected during the course of the study from the inhabitants of these homes and analyzed for three characteristic permethrin metabolites (cis-DCCA, trans-DCCA, 3-PBA).

Permethrin was detected in house dust if the wool fibers contained permethrin. Depending on the permethrin level in wool fibers, the permethrin concentrations in house dust (fraction < 2mm) ranged from < 1 to 659 mg/kg. The permethrin concentrations on suspended particles varied in most cases between < 1 and 6 ng/m<sup>3</sup>. No correlation between the permethrin concentration on suspended particles and in house dust was observed.

The metabolite concentrations in most urine samples of the studied occupants were below the limit of detection, e.g. 0.2 µg/L (percent below limit of detection (mean value first and second sampling event) cis-DCCA – 93 %, trans-DCCA – 89 %, 3-PBA – 82 %). The metabolite concentrations of the urine samples varied depending on the metabolite and sampling event. Maximal values were 2.8 µg/L for cis-DCCA, 5.1 µg/L for trans-DCCA and 5.0 µg/L for 3-PBA. In the present study, the 95. percentiles for all metabolites and sampling events were below 1.0 µg/L. Although the level of permethrin metabolites in the urine of the study population was low, the observed metabolite concentrations were substantially higher than expected from inhalational uptake as shown by model calculations.

In order to check whether children (especially crawling children) have a higher uptake of permethrin (via oral or dermal uptake of permethrin bound to house dust) the data of metabolite concentrations were analyzed with respect to age. Most people were adults, 12.8 % (13.2 %) were children 6-14 years old and 9.2 % (5.9 %) <6 years (second sampling event in parentheses). The analysis of the data demonstrates that in 23.6 % (10 %) of the adult samples at least one permethrin metabolite was found. In 33.3 % (16.7 %) of the samples in chil-

dren ranging from 6 –14 years and in 30.8 % (12.5 %) of those <6 years, a permethrin metabolite was found. However, this difference in positive urine samples between the three groups was not statistically significant ( $\chi^2$  test - first event: 0.615; second event: 0.698). This also holds true for the metabolite concentrations in urine, when the difference between the arithmetic mean values of the concentrations of cis-DCCA, trans-DCCA and 3-PBA of the three groups was proved by the Kruskal-Wallis test (first event: cis-DCCA: p=0.848, trans-DCCA: p=0.652, 3-PBA=0.308; second event: cis-DCCA: p=0.351, trans-DCCA: p=0.382, 3-PBA=0.152). Note, however, that the number of children <6 years was low.

The results of the study show that the metabolite concentrations cannot be explained by the inhalation of suspended particles. As with small children an additional oral and dermal uptake of permethrin from wool carpets is conceivable, higher concentrations of permethrin metabolites in the urine of children than in adults may be expected. This could not be confirmed by the results of the study.

Furthermore, the observed metabolite concentrations were at a similar level to that reported on the background concentration of the pyrethroid metabolites of the general population. Food is discussed as a major source for the background level. Thus, if wool carpets contribute in any way to the internal burden by pyrethroids, the contribution must be lower than the general internal burden originating from other sources.

### **Acknowledgements**

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## Areas of High Agricultural Pesticide Use in California: How Many Children Live There?

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Nationwide, 22% of pesticide use is applied in California. A public use database maintained by the California Dept of Pesticide Regulation allows pesticide use applied to fields in California to be mapped to a resolution of one square mile and allows potentially exposed populations to be identified. We overlaid this use information for several classes of pesticides, including potential carcinogens, potential reproductive agents, and organophosphates for the years 1991-1994 with 1990 U.S. census block information.

Many (61%) of census blocks had no agricultural pesticide use. "High" pesticide use census blocks groups were defined as block groups where pesticide use was greater than 1,000 pounds of pesticides per square mile of census block. For potential carcinogens, 2.6% of census blocks with a population of 92,829 children had high pesticide use. For organophosphates, 0.4% of California census blocks with a population of 33,710 children had high pesticide use. Environmental and biological monitoring data is limited and is needed in these areas to determine exposures.

### METHODS & RESULTS

*Agricultural Pesticide Use Reporting:* Since 1990, all agricultural applications of pesticides in California are reported to the County Agricultural Commissioner which then reports the data to the CDPR who maintains the California Pesticide Use (PUR) database. The PUR database provides the active ingredient, quantity applied, acres treated, crop treated, date and location of application. There are over 850 pesticide active ingredients, referred to here as pesticides, applied agriculturally in California each year. Inert ingredients, which may also be toxic, are not reported. Table 1 displays the PUR pesticides classified into toxicological and chemical groups.

**Table 1. Pesticides with reported use in California from 1991 to 1994 in toxicological and chemical groups**

#### *Toxicological Groups*

Probable carcinogens (Class B2)<sup>a</sup>: alachlor, cacodylic acid, captan, chlordane, chlorothalonil, daminozide, 1,3-dichloropropene, iprodione, lindane, mancozeb, maneb, metam sodium, orthophenylphenol, oxythioquinox, propargite, propoxur, pentachlorophenol, propyzamide and vinclozolin.

Possible carcinogens (Class C)<sup>b</sup>: acephate, acrolein, amitraz, atrazine, benomyl, bifenthrin, bromacil, bromoxynil, carbaryl, chlorthal-dimethyl, cyanazine, cypermethrin, dichlobenil, dichlorvos, diclofop-methyl, dicofol, dimethoate, ethalfluralin, fosetyl-al, hydrogen cyanamide, imazalil, linuron, methidathion, metolachlor, molinate, norflurazon, oryzalin, oxadiazon, oxyfluorfen, pendimethalin, permethrin, phosmet, phosphamidon, piperonyl butoxide, simazine, triadimefon and trifluralin.

Genotoxic compounds<sup>c</sup>: 2,4-diethylamine, acephate, alachlor, aldicarb, atrazine, benomyl, captan, carbaryl, carbofuran, chlordane, chloropicrin, chlorothalonil, chlorpyrifos, diazinon, 1,3-dichloropropene, diquat dibromide, malathion, metam sodium, methyl bromide, methyl parathion, mevinphos, orthophenylphenol, oxydemeton methyl, paraquat dichloride, pentachlorophenol, trifluralin and ziram.

Developmental or reproductive toxicants<sup>d</sup>: 2,4-diethylamine, benomyl, bromoxynil, carbofuran,

Table 1. Pesticides with reported use in California from 1991 to 1994 in toxicological and chemical groups

cyanazine, diazinon, diquat dibromide, s-ethyl dipropylthiocarbamate (EPTC), mancozeb, maneb, metam sodium, methyl bromide, methyl parathion, oxyfluorfen, propargite, s,s,s-tributyl, triadimefon and vinclozolin.

#### *Chemical Groups*

Organochlorides<sup>e</sup>: dicofol, endosulfan and lindane.

Organophosphates<sup>e</sup>: acephate, azinphos-methyl, chlorpyrifos, diazinon, dimethoate, disulfoton, ethoprop, fonofos, malathion, methamidophos, methidathion, methyl parathion, mevinphos, naled, oxydemeton-methyl, parathion, phorate, phosmet and profenofos.

Carbamates<sup>e</sup>: aldicarb, benomyl, carbaryl, carbofuran, frometanate, methomyl, pebulate and propoxur.

Dithiocarbamates<sup>e</sup>: mancozeb, maneb, metam sodium, thiram, zineb and ziram.

- a. *Probable human carcinogens with sufficient evidence in laboratory animals and inadequate or no evidence in humans from US EPA.*<sup>(1)</sup>
- b. *Possible human carcinogens with limited evidence in laboratory animals from US EPA*<sup>(1)</sup>
- c. *Positive in two or more laboratory assays from Gold and Zeiger*<sup>(2)</sup> *and US EPA.*<sup>(3)</sup>
- d. *Positive in one or more developmental or reproductive studies in laboratory animals from CDPR.*<sup>(4)</sup>
- e. *Chemical groups were identified from Meister.*<sup>(5)</sup>

*PUR Mapping by PLSS Section:* The locations of pesticide applications are reported using an identifier that represents a section within the Public Land Survey System (PLSS), a nationwide grid of approximately one square mile units termed sections. We used the 1991 – 1994 PUR data to coincide with the time period of the census. We deleted from further analysis applications with reported invalid PLSS section identifiers. The small percentage of errors (less than 1% of applications) in the quantity of pesticide applied were corrected. Map 1 illustrates the distribution of OP use in California by PLSS section.

*Mapping by census block group* We used a GIS to overlay the PLSS sections of the PUR with the 1990 US census block groups. For each block group, pesticide use density (pounds per square mile of the census block group) was calculated by averaging the pesticide use in all of the block group's PLSS sections. Map 2 is an example of this mapping in Fresno, California, an urban area with surrounding agricultural. In such areas, rural block groups tend to have the highest pesticide use density and smaller urban block groups the lowest.

Map 3 illustrates the use of probable carcinogens by census block group. In agricultural rural areas, where census block groups are geographically large, census block group mapping (Map 3) is less geographically specific than mapping by PLSS section (Map 1). The distribution of higher use areas for both California maps corresponds with the heaviest agricultural counties in the state based on farm revenues.<sup>(6)</sup>

*Population estimates:* We used 1990 census data to obtain the number of children under 15 years of age in block groups with "high" pesticide use densities. We defined "high use" as above 1000 pounds/square mile of census block group. By toxicological class, developmental and reproductive toxicants had the greatest number of children living in high use areas, with 417,000 children. For Class B (probable) and Class C (possible) carcinogens combined, this number was more than 3 fold less, around 135,000 children. By chemical class, dithiocarbamates had the greatest number of children living in high use census blocks. The variation in the number of children living in these block groups demonstrates that there were different populations potentially exposed for each pesticide group.

**Table 2. 1991 - 1994 Annual average pesticide use density and 1990 population of children under 15 in California census block groups<sup>a</sup>**

Pesticide Group	Median (lbs/mi <sup>2</sup> )	Maximum (lbs/mi <sup>2</sup> )	Block Groups (>1,000lbs/mi <sup>2</sup> )	Children (<15) (>1,000lbs/mi <sup>2</sup> )
Class B Carcinogens	31	14,395	258	92,829
Class C Carcinogens	23	5,043	122	42,389
Developmental/Reproductive Toxicants	45	48,784	1,099	381,773
Genotoxic Compounds	48	70,670	1,214	417,470
Organochlorines	9	589	0	0
Organophosphates	18	7,129	91	33,710
Carbamates	14	1,706	9	2,912
Dithiocarbamates	30	14,931	241	85,015

a. Total number of block groups used in this analysis was 21,443.

## DISCUSSION

In California, there was a wide range of pesticide use density by area (Maps 1 and 3) and by pesticide class (Table 2). The relationship between agricultural pesticide use, personal exposure and health effects has not been well defined. The limited environmental data available suggest that residents may be exposed to pesticides applied agriculturally through air, household dust and ground water.<sup>(7-15)</sup> Children living in agricultural communities could also be exposed to pesticides from playing in treated fields and eating produce directly from fields. We consider pesticide use density an indicator for all of these potential exposures.

The PUR system has limitations. Although pesticide reporting is legally mandated, under reporting has not been evaluated. The type and amount of inert ingredients applied, and residential use are not included. Structural fumigations and landscaping uses on golf courses and along highways are only included at the county level. Nevertheless, the PUR system is probably the most comprehensive pesticide use database in the world.

Our findings suggest that the hundreds of thousands of children living in high agricultural pesticide use areas have a higher potential for exposure than their more urban counterparts. Biological monitoring of pesticide levels in children indicates an inverse relationship with distance from treated orchards.<sup>(13, 17)</sup> Further environmental and biological monitoring is needed to determine the relationship between agricultural pesticide use and individual exposure. Our findings suggest geographical (Maps 1 and 3) and pesticide group (Table 2) priorities.

This evaluation suggests that the prevalence and geographic extent of agricultural pesticide use for the compounds of interest are appropriate to assign neighborhood exposure attributes for an epidemiologic study of childhood cancer. These exposure methods can be used, with some minor modifications, in other cancer studies conducted at the block group level in California or other states if pesticide use reporting systems are developed.

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