Action Programme Environment and Health

Workshop on Exposure of Children to Substances used as Ingredients in Pesticides

Berlin, 27 – 29 September 2001

Supported by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety in the framework of the Action Programme "Environment and Health"

Federal Institute for Health Protection of Consumers and Veterinary Medicine

The participants of the workshop in front of the location Dahlem of the Federal Environmental Agency in Berlin, where the first part of the workshop took place.

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I. Introductory remarks:

Children are commonly exposed to lots of chemicals occurring from private use in the residential areas. They are also representing a specific sub-population among the consumer-population. It is said that children are more sensitive towards chemicals, but this has not been considered particularly in risk assessment. The workshop, to which experts from six European states and from the US were invited, was held to prepare a compilation of knowledge and approaches of exposure assessment for children. In this context, the residential exposure to pesticides was taken as an example. One essential outcome of the workshop was to elaborate minimal requirements which are needed to perform an adequate assessment. This includes the characterisation of the use of substances and products, how they are released and transferred to the site of exposure, e.g. by residential contact after use by professionals or consumers, via contamination of indoor air, dust, soil, and food.

To address the question of children as a vulnerable population, toxicogenetics and toxicokinetics were discussed, as well as children's special behaviour, e.g. mouthing, and health effects that can be observed.

Because measurements are seldomly available to perform residential exposure assessments, models need to be developed. Data to be fed into those models need validation and approaches to gather data have to be developed..

The consideration of variability and uncertainty of the data, models, and the respective results has obtained an increased importance. The impact of statistical methodology and the advantages and limits of probabilistic assessments will be addressed.

The workshop was performed divided into three parts on three days:

At the first day, introducing lectures giving overviews of the main items were held.

At the second day, recommendations were worked out on four working groups, which were than discussed at day three in the plenum of the invited experts.

This report comprises the lectures and is giving a structured and overview on the contributions as abstracts or papers, with a link to the presentations, the working group results and conclusions.

Contents:

II. Section I (Lectures and posters)

II.1. Are children more vulnerable than adults?

II.1.1. Children versus adults: differences and similarities in response to environmental pollutants and chemical/drug poisons

Open Presentation

Wayne R. Snodgrass

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 surface 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.

Open Presentation

II.1.2. Impact of pharmacogenetics for toxicity of xenobiotics in children

Matthias Schwab

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 unterstand 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 exemplary 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 ontogency. 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 childern is the result of a complex interaction between pharmacogenetics, development,

and additionally exogenous factors (e.g. disease, nutrition). Both pharmacogenetical and developmental factors affecting the activity of xenobiotic-metabolizing enzymes should be taken into account for better understanding of toxicity of xenobiotics in children.

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.

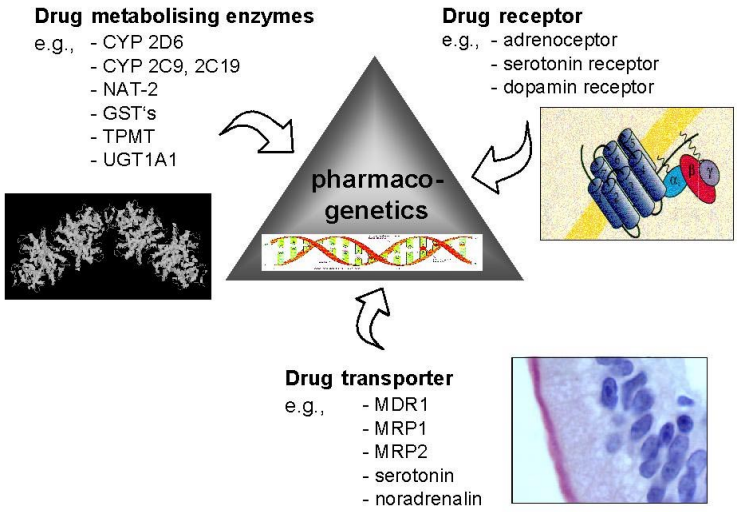


Figure 1.

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 (ultrarapid metabolizer).

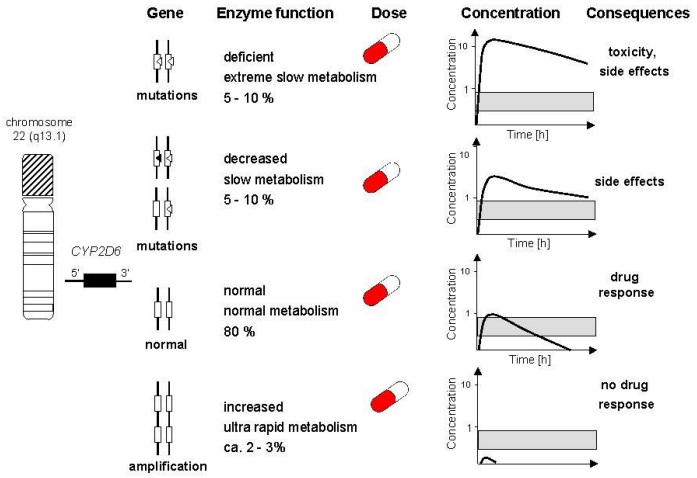


Figure 2

II.1.3. Behaviour patterns influencing exposure of children

Open Presentation

Bea Steenbekkers

Introduction

This mouthing study was set up as a preliminary research to determine the health risks for children caused by phthalates in PVC-toys. It was part of a larger Dutch project in which risks of phthalates for young children were assessed. The project carried out under the responsibility of the Dutch Consensus Group, consisted of four parts (Könemann, 1998): a human volunteers study to determine release rates of di-isononylphthalate (DINP) from PVC samples into saliva (carried out by TNO Nutrition and Food Research Institute) a child observation study to determine the oral contact time of small children with baby toys (carried out by Wageningen University) a new assessment of the exposure of babies to DINP from soft PVC specimens (carried out by RIVM, Bilthoven) development of a routine laboratory method to determine the release rate of DINP from PVC baby toys (carried out mainly by TNO Nutrition and Food research Institute, with assistance from other laboratories).

In this paper information and results of the Wageningen mouthing study are presented (for more information see also Groot et al. (1998)).

Aim of the research

The aim of the research is to quantify duration of mouthing in infants 3 to 36 months of age and to study child-to-child variation.

The term mouthing means: all activities in which objects are touched by the mouth or put into the mouth except for eating and drinking. This term includes licking as well as sucking, chewing and biting.

Children show different kinds of mouthing behaviour. The development in mouthing behaviour starts with sucking as a reflex. After some time children start to explore by putting things into their mouth. This is not necessarily sucking, but also licking, chewing and biting.

When children get older, they suck when they are tired or need comfort. It is not possible to pinpoint a part of the day in which it can be expected that children mouth more than other parts of the day. This because of the fact that each child's daily routine differs between children and some children start exploring by mouth when they are lively, others when they get tired.

Differences between children regarding the mouthing behaviour are very large. Even big differences are found in one family.

Design

In order to obtain data that are suitable to be used to reach the aim of the study, observations were done and a questionnaire was used (Steenbekkers, 2001).

The observations had to be done by a person who is familiar to the child and in a normal setting because this would least influence the behaviour of the child.

Parents were asked to observe their children ten times 15 minutes per day on two days. This means a total observation time of 2.5 hours a day. The mouthing time was measured by means of a stopwatch to get exact data. The observations took place when the child was awake during the day. No observations were done while the child was sleeping or

eating. In addition to the observations, the parents filled in a questionnaire covering demographic aspects, characteristics of the child and policy regarding the use of a dummy.

Five categories of objects are discerned: dummy/pacifier, theether, fingers, toys, non toys. The parents specified the toys involved. On the basis of this specification the toys are divided into two groups: toys meant for mouthing and toys not meant for mouthing. This division is made according to the definition producers of toys give. It should be noted that parents make this division in another way.

The children are divided into four groups according to their age (3-6 months, 6-12 months, 12-18 months and 18-36 months). Generally speaking each group is in a different phase of development.

Analysis

In order to get daily mouthing times, the sum of the observed mouthing times during one day was extrapolated to the total time awake. For this extrapolation the rhythm of the day, filled in in the questionnaire by the parents, is used to determine the time the child is awake and has the opportunity to put something into the mouth. The same procedure was followed to obtain the total frequency of hand/object to mouth contact.

Because the dummy is not made of PVC, this category is not important for this research. For this reason all presented mouthing times are the extrapolated total mouthing times without a dummy for the time awake.

Results

Data of 42 children are obtained.

The children are divided into 4 age groups, according to developmental period:

- 3 to 6 months (n=5);
- 6 to 12 months (n=14);
- 12 to 18 months (n=12);
- 18 to 36 months (n=11).

The total time of mouthing behaviour in the observational period is extrapolated to the time the child is awake and not involved in eating. This will be referred to as the ‘awake time per day’. This is the total time of a day that the child has the opportunity to put objects into the mouth.

The total mouthing time per day differs much between children, both within and between age groups. The variation is large. The results for the different age groups are given in table 1.

Table 1. Descriptive statistics of total mouthing time [minutes] excluding dummy

	standard deviation	minimum	mean	maximum
3-6 months	19.0	14.5	36.9	67.0
6-12 months	44.7	2.4	44.0	171.5
12-18 months	18.2	0	16.4	53.2
18-36 months	9.8	0	9.3	30.9

The total mouthing time, without dummy, varies in this sample between 0 minutes and approximately 3 hours. Mean total time is 26 minutes (standard deviation: 32 minutes) for all age groups taken together. Children in the youngest age group (3 to 6 months) use mostly their fingers to mouth on, whereas children in the age between 6 and 12 months of age spend most of this total time mouthing on toys (not meant for mouthing). In this latter age group largest values for total mouthing time are found. This is graphically shown in figure 1.

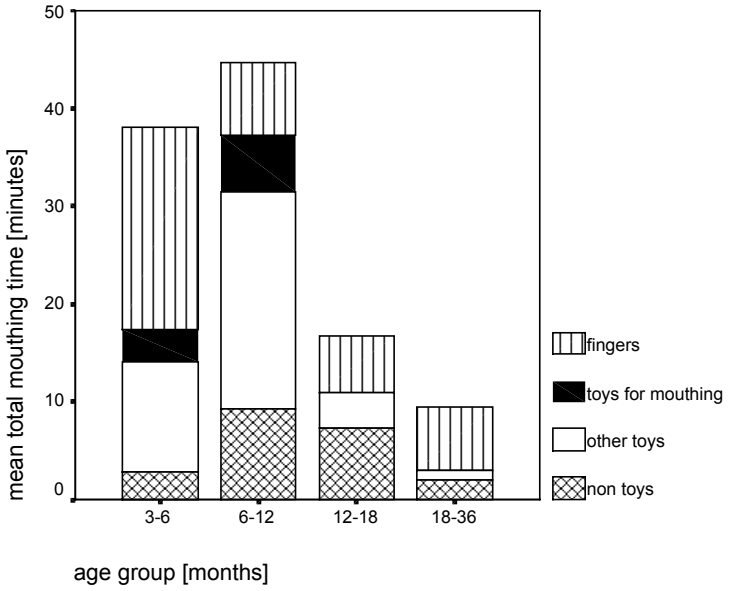


Figure 1. Mean total mouthing time [minutes] during the awake time per day, per category of objects and per age group, excluding dummy

Hand/object-to-mouth contact

The frequency of hand/object to mouth contact is assessed by counting the frequency of contact per observation period. These are added per day and extrapolated to the total time awake during the day. The correlation of the frequncy of contact between the first and the second observation day is 0.817 and statistically significant ($p<0.05$).

In table 2 the mean extrapolated frequency of contact for the two observation days is given per age group.

Table 2: Mean extrapolated frequency of hand/object to mouth contact per day.

age group [months]	mean	standard deviation
3-6	117	80
6-12	208	134
12-18	84	95
18-36	51	32

In figure 2 the frequency of contact is presented relative to the total mouthing time during the observed days. The correlation between these two variables is 0.611 and statistically significant ($p<0.05$).

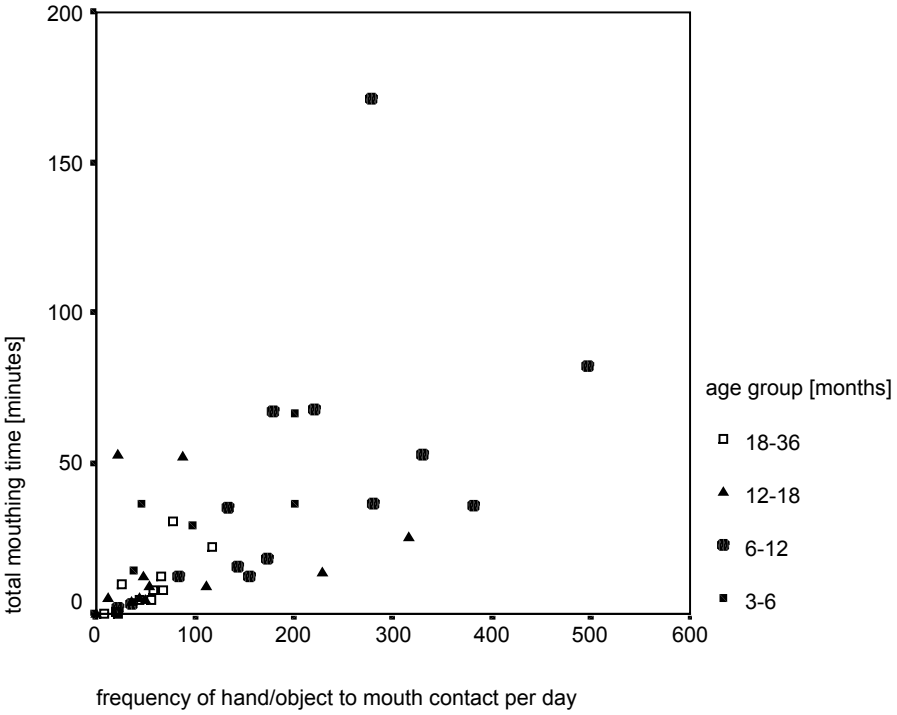


Figure 2: Frequency of hand/object to mouth contact related to the total mouthing time according to age

Conclusion

A number of methods are available to study human behaviour. When one wants to estimate the risk of use of products it is necessary to study actual behaviour in the everyday setting.

Differences in observed behaviour are large between children within the same age group, but also between age groups. This is comparable to results found in other studies on variation in human behaviour (Weegels and van Veen, 2001). On the other hand, results per child per day over two different days are rather comparable.

Children in the age group 3-6 month mouth relatively most on their fingers. They are not yet able to grab and hold products. Only products given to them are mouthed, and their fingers are always available for that purpose. The age group 6 –12 months is able to pick up things themselves and explore them by putting them into their mouth. They mouth more often on products in their surroundings. In this phase they also start getting teeth, which is an extra reason for showing mouthing behaviour.

Generally speaking the children older than one year of age appear to have less urge to mouth.

The results of the Wageningen mouthing study show that children in the age between 6 and 12 months are at highest risk when mouthing is involved. In these children a relatively low body mass and a large mouthing time are combined.

References:

1. Groot, M.E., Lekkerkerk, M.C. and Steenbekkers, L.P.A. (1998). *Mouthing behaviour of young children, an observational study*. Wageningen Agricultural University, Subdepartment of Household and Consumer Studies, Wageningen, The Netherlands. ISBN 90 6754 548 1
2. Könemann, W.H. (ed.) (1998). *Phthalate release from soft PVC baby toys; report from the Dutch Consensus Group*. National Institute of Public Health and the Environment, Bilthoven, The Netherlands.
3. Steenbekkers, L.P.A. (2001). Methods to study every day use of products in households: the Wageningen mouthing study as an example. *Annals of Occupational Hygiene*, Vol. 45, No. 1001, pp. S125-S129.
4. Weegels, M.F. and M.P. Van Veen (2001). Variation of consumer contact with household products: a preliminary investigation. *Risk Analysis*, Vol. 21, No. 3, pp. 499-511.

Open Presentation

II.2. Characterisation of pesticide exposure to children

II.2.1. Heavy metals, pentachlorphenol, pyrethroids, and allergens in house dust from children's dwellings

Open Presentation

Ulrich Franck, Olf Herbarth , Ulrike Kampzyk, Peter Krumbiegel, Andrea Müller, Martina Rehwagen, Maik Schilde, Hans-Joachim Stärk

Human exposure is characterized by a variety of pollutants. An important type of pollutants is dust. Inhalation of non-volatile and insoluble dust particles itself can lead to risks for human health. On the other hand, aerosol particles can be an important carrier for different organic compounds. In this contribution various health risks of different types of dust exposures will be demonstrated. We measured at indoor and outdoor sites, mainly close to the individual. Our investigations are focussed to children as a particular vulnerable group. The main aim of these studies was to demonstrate and evaluate the complexity of burden associated to airborne, sedimentary and house dust.

People in Central Europe spend 80% or more of their time indoors, showing that in the overall time budget the indoor environment is playing the most important role for human exposure. On this account we extensively studied indoor pollutants.

The following studies were carried out in different areas of Central Germany which are characterized by different types of pollution (former mining and smelter area / formerly heavy chemically polluted chemical industrial area), control areas and a large city.

Metals:
Some metals (e.g. heavy metals) have a well known health impact. Lead is one of the most common pollutants in the environment and especially dangerous for unborn and young children. Nowadays, lead in drinking water has lost it's importance with respect to total lead burden of the population in East Germany. As some areas of East Germany (especially Central Germany) are thought to be highly polluted by a variety of chemicals, monitoring the lead burden among children is of major importance.

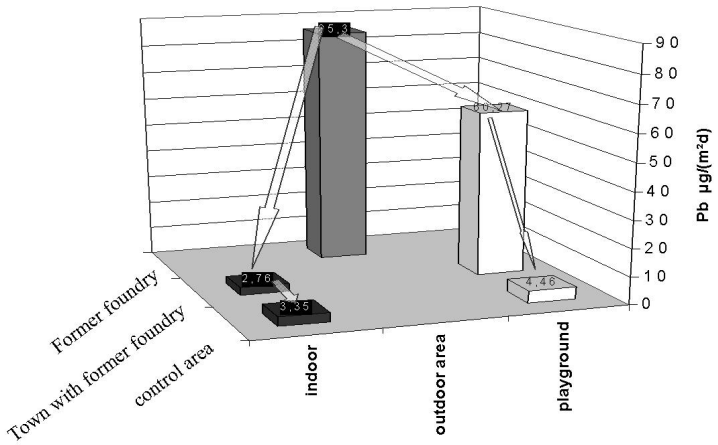


Figure 1: Lead in sedimentary dust (former foundry site; kindergardens in the town with the for-mer foundry and in the control area - indoor/ outdoor)

We compared sampling sites in a former mining and foundry town, in sites which are polluted rather by organic compounds than metals, and in control areas. The mass of airborne and sedimentary dust does not differ significantly between the sampling sites (industrial/control areas). On the other hand, a much higher exposure by metals could be detected in the former mining area. A significantly higher burden was found in the former mining and smelter area.

The concentration of lead in sedimentary dust decreases with increased distance from the former foundry (Fig. 1) The concentration of metals in house dust from children's dwellings are higher in the neighborhood of the former foundry. The higher concentrations of metals in airborne, sedimentary outdoor and indoor dust are related to higher concentrations of metals in house dust.

The (external) exposure of children to metals causes higher internal burden by metals. This is demonstrated by increased lead concentrations in the deciduous teeth of children (Fig. 2). The concentration in the teeth is a measure of past exposure and especially of chronic and low level exposure. Moreover, the decay of the lead concentration within this hard tissue can be neglected. Consequently, the deciduous teeth represent a dosimeter, sampling from the beginning of the mineralization of the teeth up to the loss.

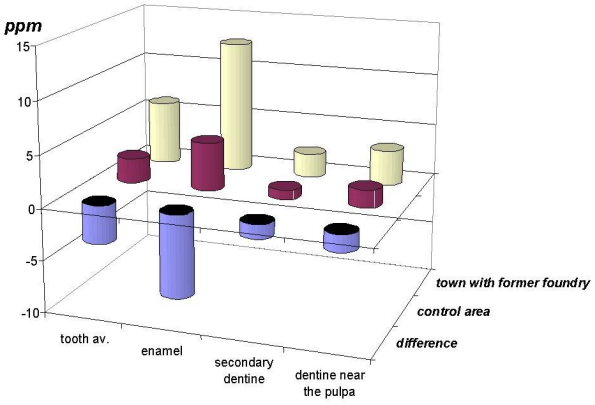


Figure 2: Lead concentrations in different parts of deciduous teeth of children from the town with the former foundry and from the control area

Mould:
Mould, especially mould spores and microbial volatile organic compounds (MVOC) produced by mould can be involved in the development of allergic diseases. The frequency of mould increased within the last years and enforced energy saving.

Type and frequency of mould species in the rooms where the children live were studied. According to air sampling Penicillium and Aspergillus were assumed as typical "indoor fungi". Penicillium and Aspergillus occurred in smaller numbers in summer than in the other seasons. In contrast, highest concentrations of total spores in house dust (predominantly Cladosporium) and yeast were found in summer.

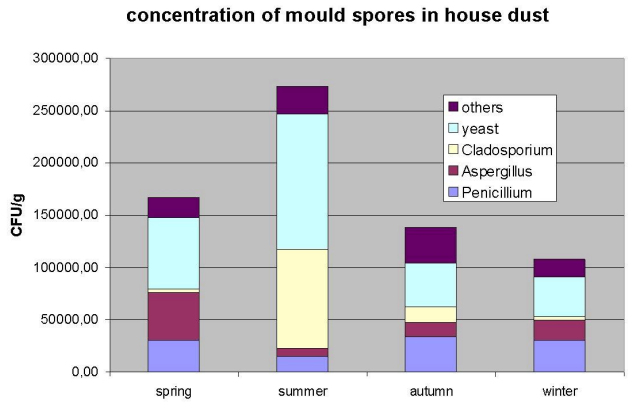
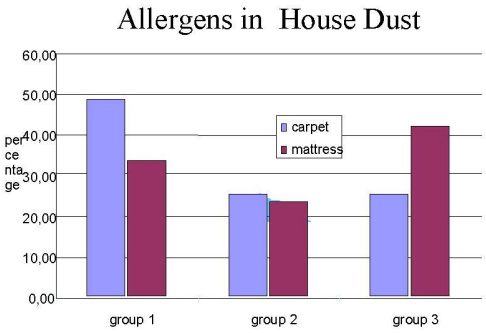


Figure 3: Concentration of mould spores in house dust from children's rooms

Dust Mites:
Dust mite allergens are well known to provoke numerous allergies. The concentration of dust mite allergens changes with seasons. The rather high concentrations of allergens in the mattresses in the winter time may be caused be the other type of bed covering used in this season. The categorization into different groups of exposure shows the high frequency of critical concentrations of dust mite allergens (Fig. 4).



group	sum Der p1+Der f1	effect
3	sum > 10 µg/g	allergic symptoms
2	10 µg/g > sum > 2 µg/g	possibility of sensibilisation
1	sum < 2 µg/g	

Figure 4: Abundance of mite allergens in house dust from children's rooms

In 27 % of investigated carpets and 48 % of mattresses allergen concentrations higher than 10µg/g dust were found.

Exposure to mite allergens was found to be associated with wheezing and atopic sensitisation to mite allergens.

Pyrethroids:
Interestingly, the concentration of pyrethroids did not increase in former East Germany

after reunification. Permethrin is the mostly used pyrethroid in household. It was most frequently found in the dwellings.

Most of house dust and urine had concentrations in the range of reference area legally for the general population. There was no correlation between the use of pyrethroids (questionnaires) and the concentrations in the house dust. The differences between the house dust and urine samples of “East“ and “West“ Germany were not significant.

West 90/91	East 91/92	Leipzig 99	
3,710	1,020	0,905	arithmetric mean
0,23	0,16	0,3	geometric mean
39,4	7,4	7,945	98th percentile
287	48	21	max

Table 1: Statistical values of pyrethroid concentrations in west Germany vs. east Germany, Leipzig

Permethrin	98,8 % of samples
Bioallethrin	84,5 % of samples
Deltamethrin	88,2 % of samples
Tetramethrin	97,5 % of samples

Table 2: Occurrence of pyrethroids in children’s rooms. Concentration above the detection limit for pyrethroids

PCP:
A correlation of the content of PCP in house dust and urine also could not be established. Because of the lack of between urine and dust concentrations of the PCBs for an individual risk assessment of PCB burden, dust measurements are not sufficient. The determination of the internal load by PCB‘s is the preferable method for individual risk assessment. Lower concentrations in house dust samples and urine samples of children in Leipzig were found, compared with small-towns.

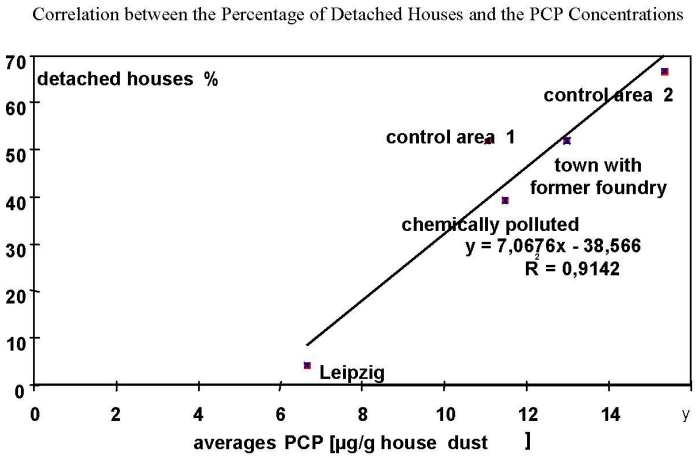


Figure 5: High PCP concentrations are correlated with the percentage of detached houses.

The differences between the house dust and urine samples of “East“ and “West“ Germany were not significant.

The chain from exposure to internal burden to (metabolic) effect can be revealed: Increased perchloroethylene concentrations produce increased concentration of trichloroacidic acid in the urine. The burden leads to a decreased detoxification capacity which can be seen by the slower elimination of methacetine.

At given mass concentrations the number concentrations increase dramatically with decreasing particle diameter. The total particle surface (responsible for absorption of organic compounds) also increases rapidly. Because of the time budget the knowledge of indoor particle concentration is essential for the risk assessment of this type of pollutant, too.

The particle size distribution of indoor particles is different from outdoor ones. The indoor atmosphere is generally shielded against outdoor particles, leading to lower number concentrations indoors than outdoors, if no important indoor sources are present: Unlike the decrease in mass concentrations of larger particle fractions, the decrease in the number concentrations of submicron and even more ultrafine particles is not linear. In the absence of significant indoor sources exist sophisticated correlations between outdoor and indoor concentrations. Therefore, to differentiate the health effects of particles of different diameters, the different decrease in the particle number concentrations in dependence on the particle sizes must be taken into account if indoor concentrations cannot be measured and outdoor concentrations are used as surrogate of indoor measurements.

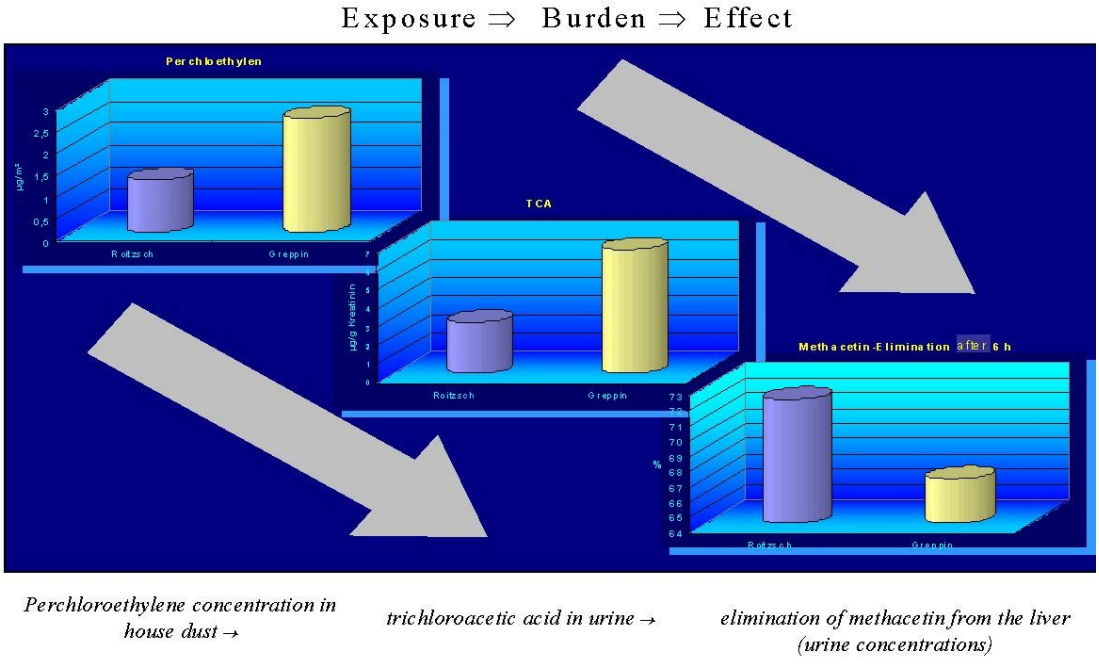


Figure 6: Pathway of perchloroethylene from house dust to humans

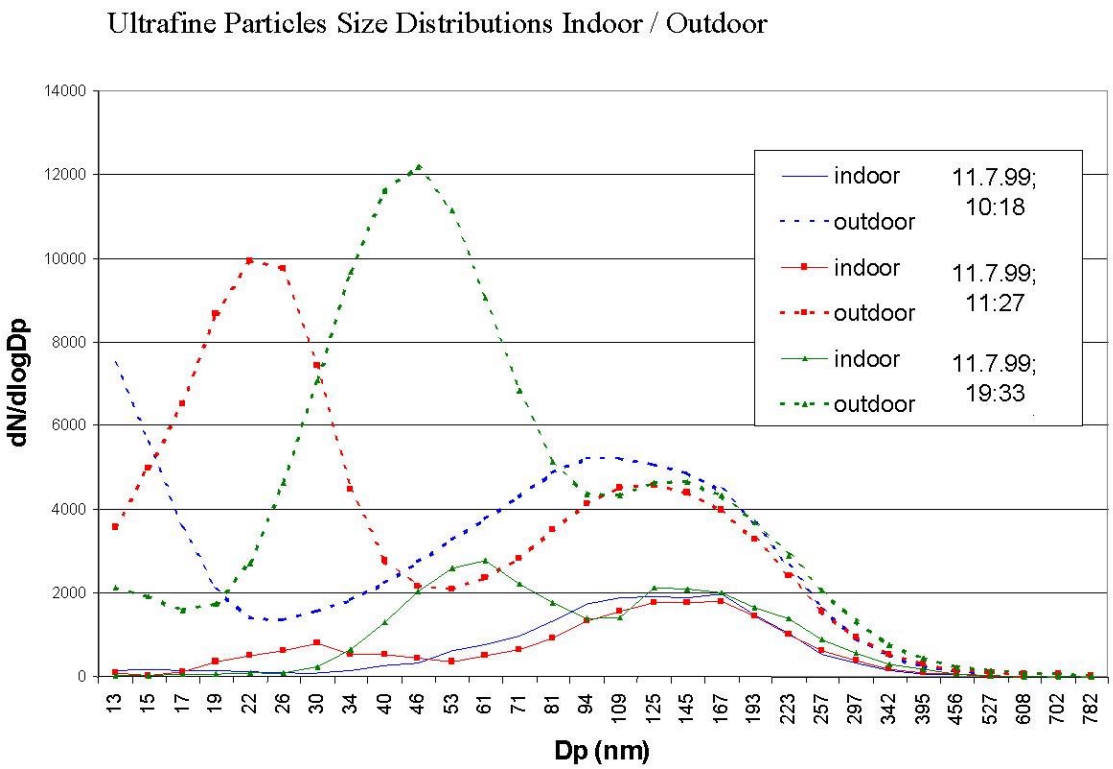


Figure 7: Ultrafine particles size distributions indoor / outdoor

Open Presentation

II.2.2. Pathways of pesticide exposures for children

Katinka van der Jagt

Open Presentation

II.2.3. An overview and characterization of the use of pesticides in German households

Jutta Herrmann

Progress in sampling and analysis and the standardisation of these procedures enable improvements in exposure analysis. For the identification of the sources of substances found in the indoor environment it is important to know the route by which the toxic pollutants get into the houses. Most of them are carried in by impregnated industrial materials such as residues of plant protection products in food, impregnated clothes, carpets and other fabrics and treated furniture, wall paper and many other commodities. This presentation focusses on those pesticide products which are bought and used by the residents themselves and those applied by professional pest control operators (PCO's) in private homes.

The pesticides used in households belong to different groups of products with very different regulative standards. Three main groups can be distinguished:

1. non-agricultural biocides (regulated by Biocides Directive(98/8/EC))
2. Human and veterinary medicines (ectoparasitic) (regulated by Medicines Act)
3. plant protection products (regulated by the Plant Protection Act)

There is a lack of data about the amount of substances used in German households. One source of data is the German Agricultural Chemical Industry Association (IVA). This organisation represents around 70 % of the companies producing or selling non-agricultural pesticides on the German market.

Table 1 is taken from the annual report for 2000 from the IVA. It gives data on the total amount and sales of active substances in pest control products for the use in households, with separate mention of professional uses. The private household uses play the major role, only around 15 % of the sales are due to PCO's. A second interesting point in the report is the decline of active substances from 1999 to 2000 but the increase in sales. This is due to the development of new, very efficiently acting substances, or new combinations of substances or different application measures.

To achieve the desired effect of a pesticide product it is important that not only the active ingredients are effective against the target organisms, but also the formulation type. The latter is important for the efficacy and it determines the degree of contamination of an indoor environment. Formulations and application forms with a broad contamination risk are: aerosols, fogs, dusts (if used in large areas/surfaces). Formulations/applications with a lower risk because of a limited contamination of small areas in an apartment /building are baits, foams, crack-and-crevice-treatments or sticks.

Concerning the patterns of use of pesticides in households there are 3 main problems:

- the widespread use of easily accessable and applicable high risk products ,
- the unqualified use of products not according to the label precautions and directions and
- the fact that many of the pesticide-applications in private homes are not necessary.

Table 1: Sales of pest control products for the use in private homes in 1999 and 2000

	sold amounts of active substances in tons					
			changes in	**portion for profes-sional use**		**changes in**
group of active sub-stance	**1999**	**2000**	**%**	**1999**	**2000**	**%**
organophosphates	*25,3*	*22,2*	*–12,3*	*6,8*	*3,9*	*– 42,6*
alpha-Cyano-pyrethroides	*0,1*	*0,4*	*300,0*	*0,1*	*0,3*	*200,0*
other pyrethroids	*2,0*	*2,7*	*35,0*			
pyrethrines	*2,7*	*2,6*	*– 3,7*			
pheromones	*0,2*	*0,4*	*100,0*			
other natural products	*20,9*	*18,7*	*–10,5*	{1,0	{0,7	{–- 30
rodentizides	*1,4*	*1,3*	*–7,1*	*0,2*	*0,5*	*150,0*
synergists	*8,9*	*10,0*	*12,4*	*0,7*	*1,4*	*100,0*
others	*13,0*	*12,0*	*–7,7*	*1,1*	*1,1*	*0,0*
all groups in tons (t)	*75,1*	*70,3*	*– 6,4*	*9,9*	*7,9*	*– 20,2*
sales in Mio. D-Mark	*98,8*	*109,0*	*10,3*	*16,4*	*18,1*	*10,4*

(source: IVA, „Jahresbericht 2000“)

II.3. Health effects in children from pesticide exposures

II.3.1. Epidemiology of pesticide poisoning - Identification of health hazards to pesticide exposures

Open Presentation

Nida Besbelli

Background

Growing concern about poisoning by pesticides has lead to actions aimed at promoting their safe use and reducing adverse effects on health. In view of the interest expressed on pesticide poisonings by medical and other professionals, regulatory authorities in countries, chemical industry, international organizations and aid programmes to developing countries, the IPCS decided to undertake formal studies, to develop statistics that may reflect the world situation. In this regard, activities of the IPCS developed with poisons centres and other partners have become highly relevant for the harmonized and comparable collection of data on pesticide poisonings .

In 1992, a consultation was convened by the IPCS with experts in the area of pesticide poisoning. The purpose was to develop a specific project for collecting data on pesticide poisoning on an international basis, with a view to establishing a sounder information base to assess the global incidence of pesticide poisoning. The initial steps were to design standard formats for collecting pertinent information on cases of poisoning. Following further consultations in 1996 and 1997, a pilot study was undertaken in three countries to test both a simple and a more elaborate data collection format. Countries with an agriculture-based economy, with a reasonably developed product registration system and infrastructure for data collection and analysis were selected for this phase of the study (India, Sri Lanka and Uruguay).

Objective

Overall objective of the project is to estimate the extent of human exposure and poisoning in selected regions/countries, with a view to implementing preventive and education strategies to reduce morbidity and mortality from pesticide poisoning. This will be achieved through:

- study of toxic exposures
- setting up surveillance mechanisms and databases on pesticides;
- training within the health sector; and
- awareness raising through public education and prevention campaigns.

Guidance documents

On the basis of the experience gained during pilot data collection studies, a form was prepared in 1997 to record patient data: “Pesticide Exposure Record” (PER). For severity grading, the classification system Poisoning Severity Score (PSS) developed by IPCS in cooperation with the European Commission and the European Association of Poison Centers and Clinical Toxicologists is used. PSS is a classification scheme for cases of acute poisonings which takes into account the observed clinical symptoms and signs. It is a standardized scale for grading the severity of poisoning which allows qualitative evaluation of morbidity caused by poisoning, better identification of real risks and comparability of data. Severity grades are as follows:

Severity grading of poisonings

(0)	NONE	No symptoms or signs. Vague symptoms judged not to be related to poisoning
(1)	MINOR	Mild, transient and spontaneously resolving symptoms or signs
(2)	MODERATE	Pronounced or prolonged symptoms or signs
(3)	SEVERE	Severe or life-threatening symptoms or signs
(4)	FATAL	Death

Current studies

On the basis of the experience gained and the data collected through this exercise, the tools developed (formats, strategy and methodology used) were assessed, discussed and improved. The material prepared was presented to representatives of countries of the WHO South East Asia Regional Office (SEARO) ,Western Pacific Regional Office (WPRO) and Americas Regional Office (AMRO/Mercosur) at regional workshops held in New Delhi, India , Singapore and Montevideo, Uruguay in from 1999 to 2001. Harmonised Case Data collection using the proposed methodology is being implemented in selected areas from countries in SEARO, WPRO and AMRO.

Regional activities - SEARO

Four countries in SEA Region, namely India, Indonesia, Nepal and Thailand have completed the Trial Implementation Phase of the project. Although the coverage and duration of this trial phase differed between the countries, data were collected using a harmonised pesticide exposure record (PER) format, medical staff was instructed on the collection of information, on the diagnosis and treatment of cases of pesticide exposure and on the use of the poisoning severity score (PSS). Guidance was given on developing a pesticide product register.

Some results and conclusions of stage 1 (trial) studies, period covered, number of cases and circumstances of exposure, PSS and outcome are given in Tables I, II, III and IV.

Expected outputs

The expected outputs of the project include:

- Database on Pesticide Product Composition
- Report on “Health Effects of Pesticides”
- Annual reports on human pesticide exposures and their characteristics
- Establishment of an international mechanism for toxicovigilance and surveillance systems for pesticide poisonings
- Identification of hazardous pesticide formulations within countries
- Prevention of pesticide poisonings through public awareness and prevention campaigns
- Recommendations for action at the health care level (and other, if relevant)

Table 1: Results and Conclusions of Stage 1 Studies

Country	Duration	Participation	Number of cases
India	1 year	10 hospital	1531
Indonesia	6 months	7 hospitals,1h.office	126
Nepal	6 months	4 hospitals, 1 h. inst.	258
Thailand	3 months	10 hospitals	130

Table 2: First Stage Studies-Circumstances of Exposure

Country	Intentional exposure	Accidental exposure	Occupational exposure
India	1304 (85.0%)	72 (4.7%)	83 (5.2%)
Indonesia	54 (44.4%)	20 (15.9%)	47 (31.7%)
Nepal	236 (91.5%)	3 (1.2%)	16 (6.2%)
Thailand	80 (61.5%)	10 (7.7%)	37 (28.5%)

Table 3: Poisoning severity score

Country	None	Minor	Moderate	Severe	Fatal
India	81	401	504	459	347
Indonesia	4	73	42	5	3
Nepal	14	66	107	61	41
Thailand	8	74	11	19	14

Table 4: Outcome

Country	Recovery %	Death related %	Unknown %
India	953 (62.3)	347 (22.7)	213 (13.9)
Indonesia	122 (97.6)	3 (2.4)	1 (0.8)
Nepal	197 (76.4)	42 (16.3)	19 (7.4)
Thailand	90 (69.2)	14 (10.7)	19 (14.6)

Open Presentation

II.3.2. Current internal exposure to pesticides in children in Germany: data on organophosphate and pyrethroid pesticides.

Ursel Heudorf, Jürgen Angerer

Introduction:

Human biomonitoring is an excellent tool for assessment of exposure to different substances, if suitable methods are available to detect those substances or their metabolites in biological material such as blood or urine specimen in a specific and sensitive way (1, 2). With regard to organophosphate and pyrethroid insecticides, such methods have been established in recent years (3, 4), and data on background exposure in adults in Germany (5-7) as well as elsewhere (8-11) have been published. Dietary intake of pesticides is thought to be the predominant source of pesticide exposure in the population. Children, however, are considered to be at risk from additional exposure to pesticides via contaminations in the house due to their hand to mouth behaviour and thus ingestion of household dust.

Methods:

Here, the data of current background exposure to organophosphate and pyrethroid pesticides in more than 300 children under 6 years of age are presented. The data are part of a large voluntary study of environmental medicine, which was conducted in Frankfurt am Main, Germany, 1998 (12-14). In the children´s homes recent indoor pesticide application had been excluded by questionnaire. In household dust specimen tested for organophosphate and pyrethroid pesticides chlorpyrifos and permethrin were the main contaminants found. Analyses for urinary metabolites of pesticides were done using well established and sensitive methods, using GC/MS (3, 4). The children´s spot urine samples were tested for six metabolites of organophosphates (dimethylphosphate (DMP), diethyl-phosphate (DEP), dimethylthiophosphate (DMTP), diethylthiophosphate (DETP), dimethyldithio-phosphate (DMDTP) and diethyldithiophosphate (DEDTP) and for four pyrethroid metabolites (cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclo-propanecarboxylic acid (Br2CA), cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propane-carboxylic acid (cis-Cl2CA and trans-Cl2-CA) and 4-fluoro-3-phenoxy-benzoic acid (F-PBA).

Results:

In 92 % of the children´s urine samples metabolites of organophosphates were found, and in 66 % of these samples pyrethroid metabolites were above the limit of detection. Levels of urinary metabolites of organophosphate insecticides were more than hundredfold higher than levels of pyrethroid metabolites (Tab. 1) Levels of urinary methylphophosphate metabolites were about tenfold higher than those of ethylphosphate metabolites. With respect to pyrethroid metabolites, levels of trans-Cl2CA were about twice the levels of cis-Cl2CA. Internal background exposure (P95) to dialkylphosphates was 621 µg/g creatinine and background exposure (P95) to pyrethroids was about 2,9 µg/g creatinine. No statistically significant seasonal variations in the urinary levels of metabolites of organophosphates and pyrethroids were to be seen (Figure 1 a, b).

Table 1: Organophosphate and pyrethroid metabolites (µg/g creatinine) in urine samples of children < 6 years of age

	% > LOD	Mean±S.D.	Range	P25	P50	P75	P 95
Organophosphates*							
DMP	77	63.4±117,6	<LOD-1096	8.8	27.4	65.7	242.0
DMTP	86	77.4±167.2	<LOD-1800	9.2	28.9	69.7	334.4
DMDTP	33	4.9±26.9	<LOD-424.7	<LOD	<LOD	2.0	24.1
Sum methylmetabolites	*88*	*145.8±273.5*	*<LOD-2620*	*23.4*	*57.6*	*148.2*	*594.0*
DEP	77	8.4±12.1	<LOD-79.1	1.3	4.8	9.3	31.4
DETP	45	4.0±12.7	<LOD-115.5	<LOD	<LOD	2.8	15.7
DEDTP	3	0.02±0.14	<LOD-1.5	<LOD	<LOD	<LOD	<LOD
Sum of ethylmetabolites	*78*	*12.4±22.2*	*<LOD-192.8*	*1.8*	*6.0*	*13.3*	*51.2*
Sum of organophosphate metabolites (µg/g crea)	*92*	*158.1 ± 284.2*	*<LOD-2636*	*23.8*	*66.6*	*158.8*	*621.6*
Pyrethroids**							
Cis-Cl2-CA	26	0.11±0.32	<-4.0	<LOD	<LOD	0.09	0.60
Trans-Cl2-CA	64	0.47±0.98	<-14.7	<LOD	0.30	0.55	1.82
Br2-CA	21	0.10±0.45	<-6.56	<LOD	<LOD	<LOD	0.51
F-PBA	20	0.09±0.24	<-1.96	<LOD	<LOD	<LOD	0.61
Sum of CA-pyrethroid-metabolites (µg/g crea)	*66*	*0.69±1.38*	*< - 18.2*	*<LOD*	*0.39*	*0.71*	*2.92*

* n= 309; ** n= 331

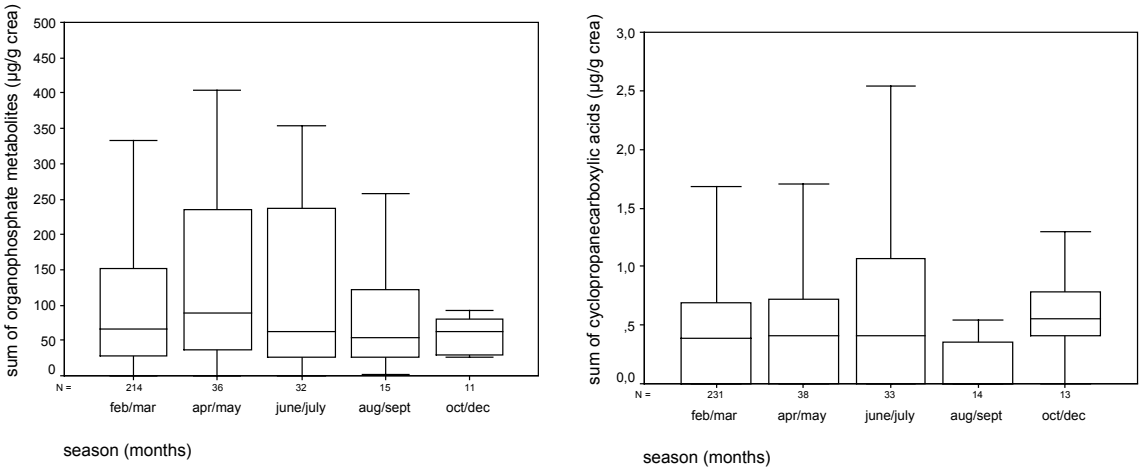


Figure 1 a, b: Organophosphate and pyrethroid metabolites found in urine specimens of children under 6 years of age (µg/g creatinine) in different months of the year

Levels of chlorpyrifos and permethrin in household dust were in the same range (chlorpyrifos 0.49±1.72 mg/kg, maximum value 14.9 mg/kg; permethrin 0.66 ± 2.95 mg/kg, maximum value 36.9 mg/kg). No hints were found for an association of levels of chlorpyrifos or permethrin in household dust with the levels of their specific urinary metabolites of the children living in these homes (Tab. 2).

Table 2: Assessment of associations of internal exposure of children under 6 years of age with specific pesticide levels in housedust of their homes

Pesticides in housedust	Specific urinary metabolites	Number	Correlations		Chi-Quadrat-test	
		N	r	p	Chi-Q	p
Chlorpyrifos	DEP	230	-0.050	0.446	2.6	0.462
	DETP	230	-0.010	0.883	4.3	0.224
	Sum ethyl	230	-0.051	0.439	3.0	0.383
Permethrin	CisCl2CA	247	0.022	0.735	2.7	0.439
	TransCl2CA	247	-0.089	0.161	4.1	0.248
	Cis and trans Cl2CA	247	-0.076	0.233	3.8	0.291

Conclusion:

Methods for human biomonitoring for organophosphate and pyrethroid insecticides are available with detection limits low enough to detect organophosphate metabolites in about 92 % and pyrethroid metabolites in about 66 % of the children. Internal background exposure of children (P 95) to dialkylphosphates was 621 µg/g creatinine and background exposure to pyrethroids was about 2.9 µg/g creatinine. Dietary intake of pesticides is thought to be the predominant source of exposure of the population to pesticides. A significant seasonal variation in the excretion of pyrethroid and organophosphate metabolites was not found in our study; this is obviously caused by the perennial availability of all food stuffs (vegetables and fruit). Though children under 6 years of age are considered to be at risk for additional exposure to pesticides via household dust by hand to mouth activity while playing on the floor, no hints were found for an association of internal exposure of children to the levels of contamination in their homes (household dust).

According to the exposure assessment of the Food and Drug Administration FAO, about 5-10 µg organophosphorous insecticides are consumed per day (15, 16). Comparative data for Germany are lacking, as well as data for pyrethroid exposure via nutrition. Confirming other environmental studies (5, 8, 9), however, excretion of organophosphorous metabolites in urine was exceeding the estimated dietary intake several fold. This discrepancy demands further investigation. It was hypothesized that due to i.e. light energy or bacterial activity degradation to the metabolites might occur on the food stuff already. Therefore, instead of „parent“ organophosphorous insecticides, which hence would be no longer detectable, consumers might ingest metabolites, which are not tested by the food controllers. Ingestion of high amounts of – up to now not detected and not analysed - metabolites may then be the cause of the high urinary organophosphate metabolite excretion of the population (5). Further investigations are necessary to test this hypothesis .

References:

1. Institute for Environment and Health: Report No R5: The use of biomarkers in environmental exposure assessment. Leicester, 1996
2. World Health Organisation: Guiding principles for the use of biological markers in the assessment of human exposure to environmental factors – an integrative approach of epidemiology and toxicology. Report on a WHO consultation, Cracow, 1993.
3. Hardt J, Angerer J: Determination of dialkylphosphates in human urine using gas-chromatography-mass spectrometry. J Anal Toxicol (2000) 24: 678-684.
4. Angerer J, Ritter A. Determination of pyrethroid metabolites of pyrethroids in human urine using solid-phase extraction and gas chromatography-mass-spectrometry. J Chromatography (1997) 695: 217-226.
5. Angerer J, Hardt J. Excretion of organophosphate metabolites in the general population (in German). Arbeitsmed Sozialmed Umweltmed (1997) 32: 470-47
6. Butte W, Walker G, Heinzow B (1998) Reference values for urinary concentrations of the metabolites of permethrin Cl2-CA (3-(2,2-Dichlorvinyl)-2,2-dimethylcyclopropanecarboxylic acid) and 3-PBA (3-phenoxybenzoicacid) (German) Umweltmed Forsch Prax 3: 21-26 (1998).
7. Hardt J, Heudorf U, Angerer J. Exposure of the general population to pyrethroids (German) Umweltmed Forsch Prax (1999) 4: 54-55
8. Aprea C, Sciarra G, Orsi D, Boccalon P, Sartorelli P, Sartorelli E: Urinary excretion of alkylphosphates in the general population (Italy). Sci Tot Environ (1996) 177: 37-41 (1996)
9. Aprea C, Strambi M, Novelli MT, Lunghini L, Bozzi N. Biologic monitoring of exposure to organophosphorous pesticides in 195 Italian children. Environ Health Perspect (2000) 108: 521-525.
10. Lu C, Knutson DE, Fisker-Andersen J, Fenske RA: Biological monitoring survey of organophosphorous pesticide exposure among preschool children in the Seattle metropolitan area. Environ Health Perspect (2001) 109: 299-303.
11. Oglobline AN, Elimelakh H, Tattam B, Geyer R, o´Donnell GE, Hold: Negative ion exchange ionization GC/MS-MS analysis of dialkylphosphate metabolites of organophosphate pesticides in non-occupationally exposed subjects. Analyst (2001) 126: 1037-1041.
12. Heudorf U, Angerer J: Internal exposure to PAHs of children and adults living in homes with parquet flooring containing high levels of PAHs in parquet glue. Int Archives of Occupational and Environmental Health (2001) 74: 91-101
13. Heudorf U, Angerer J: Metabolites of pyrethroid insecticides in urine specimens: current exposure in an urban population in Germany. Environmental Health Perspectives (2001) 109: 213-217.
14. Heudorf U, Angerer J: Metabolites of organophosphorous insecticides in urine specimens from inhabitants of a residential area. Data from the former American Forces housing estates in Frankfurt am Main, Germany. Environmental Research (2001) 86:80-87.
15. Gunderson EL: FDA Total Diet study, july 1986-april 1991, Dietary intakes of pesticides, selected elements and other chemicals. J AOAC Int (1995) 78: 1353-1363
16. Yess NJ: Residue monitoring 1991 – Food and Drug Administration Pesticide Program. J AOAC Int (1991) 75: 135A-157A.

II.3.3. Health effects from exposure to pesticides in Germany

Open Presentation

Herbert Desel

Objective:

Poison centres (PCs) give advice in most acute exposures to all kinds of products and natural organisms. PCs keep record of all cases in which they are involved in electronic databases which can be searched for epidemiological studies. A basic set of information is recorded for all cases, a selection of cases (with well defined patient's history) is followed up carefully with respect to symptoms and outcome. The frequency of pesticide exposures and the character of pesticide-related intoxications in childhood is investigated in North Western Germany.

Method:

The GIZ-Nord poison centre's database is searched for cases with exposure during the years 1996-2000, especially for cases with exposures to pesticides in children. The number of exposed human beings was calculated by eliminating calls without human exposure from the data set and correcting cases with more than one patient. Age groups for detailed analysis were children (below 10 years) and juveniles (10 to 18 years old) according to the harmonised EU – recommendations for poison centre reports (1). Product names recorded in the database were classified according to a category system developed in the German research project EVA (2). Severity of clinical symptoms was scored using the IPCS poisoning severity score (PSS) (3).

Results:

The GIZ-Nord poison centre provides service for 12,800,000 inhabitants in North Western Germany. In the time between 1996 and 2000, in total 108,558 calls were answered and recorded (1,696 calls / 1,000,000 inhabitants per year). 52 % of all calls were received from the general public, 46 % from medical doctors, and 2 % from other health professionals. During the period under investigation 99,109 patients had experienced any exposure, including 48,746 children and 6,485 juveniles.

In Tab. 1 an analysis of the products involved in exposures is presented. Most of the exposures are with medical drugs (38.3 %), chemical products (23.4 %), and plants (13.0 %). 2,968 exposures with pesticides were recorded. In 1,095 cases, children were exposed and in 65 cases juveniles. This corresponds to 3.0 % of all exposures and 46 exposures per year and million inhabitants served (2.2 % for children).

Table 1: products in all exposures (GIZ-Nord, 1996 - 2000)

Product type	% of all exposures
medical drugs	38.3
chemical products	23.4
plants	13.0
food, beverages, tobacco	6.1
cosmetic products	4.5
pesticides	**3.0**
others	11.7

Children's pesticide exposures were analysed for the type of pesticide involved (Tab. 2 a). More than half (56.6 %) of all cases were exposures with insecticides, while rodenti-

cides contribute to 18.4 %. Pesticide subcategories with most exposure were alkyl phosphates (353 cases, 32.2 %), pyrethroids (107 cases, 9,8 %), and anticoagulant rodenticides (104 cases, 9.5 %).

Table 2: Pesticide Exposures in Children (GIZ-Nord, 1996 - 2000)

a)			b) N° cases			
	% of all children's pesticide exposures		with symptoms	without symptoms	evaluation not possible	total
insecticides	**56.6**		85	526	9	620
alkyl phosphates		*32.2*	37	311	5	353
pyrethroids		*9.8*	19	87	1	107
chlorinated hydrocarbons		*1.3*	6	7	1	14
carbamates		*1.1*	4	8	0	12
others or unknown		*12.2*	19	113	2	134
rodenticides	**18.4**		32	156	14	202
anticoagulants		*9.5*	11	87	6	104
phosphides		*1.9*	4	16	1	21
others or unknown		*7.0*	17	53	7	77
repellents	**6.7**		10	61	2	73
herbicides	**6.3**		20	47	2	69
fungicides	**3.7**		12	27	1	40
molluscicides	**3.7**		7	31	2	40
wood protection products	**3.0**		10	23	0	33
seed disinfectants	**0.8**		0	9	0	9
Others or unknown	**0.8**		0	9	0	9
In total ...	**100.0**		**176**	**889**	**30**	**1,095**

Children's pesticide exposures were further analysed with respect to the severity of symptoms observed (Tab 2 b):

1065 cases (97.3 % of the total number of children's pesticide exposures) could be scored for severity of symptoms:

- In **889 cases** (83.5%) no symptoms were reported, while in **176 case**s (16.5 %) at least minimal symptoms were observed and reported.

Cases with symptomatic patients were evaluated for the degree of poisoning according to the Poisoning Severity Score (PSS):

- **No severe intoxications** were observed; there were **no cases** with **lethal outcome**.
- **7 patients** (0.7 %, 1,4 cases per year) had **moderate** symptoms: two cases concerning insecticides, three rodenticides, and one case each concerns a herbicide and a wood protection product. From the description of the patients' history and symptoms

observed (Tab. 3) the routes of exposure and absorbed doses can roughly be estimated: The exact exposures were low or unknown in all these cases.

- **169** (15.9 %) pesticide exposed **children** suffered from **minor symptoms**.

Table 3: Cases with Moderate Symptoms After Pesticide Exposures in Children (GIZ-Nord, 1996 - 2000)

- Parents reported that their 6 month old boy became apnoic for 30 sec after an episode of crying. Two weeks before the family's apartment had been (professionally) treated with 7 l of a **insecticidal** solution containing fenitrothion, pyrethrum, and piperonyl butoxide.
- A 1½yo girl developed hemorrhagic diarrhea for two days after licking an ant-trap with unknown **insecticidal** incredients.
- At night, a 2½yo boy developed a series of three seizures. The ground around the family's house was treated with an anticoagulant-type **rodenticide** product.
- A 6yo boy suffered from seizures, was afterwards disoriented and developed cyanosis after oral uptake of an unknown dose of unknown **rodenticide**.
- A 3yo girl was found stuporous with open eyes, not reactive to verbal stimuli. A relation with an oral uptake of an unknown dose of an unknown **rodenticide** was questioned.
- Parents reported that their 8y boy inhaled an unknown dose of a **fungicide** containing azoxystrobin and developed a strong allergic reaction (unknown type).
- A 2½yo girl developed a seizure while playing in wooden sand-box which was treated with a **wood protection** product containing furmecyclox, dichlofluanid, and permethrin. Later she suffered from diarrhea.

In Tab. 4, all symptoms reported to the poison centre are compiled. Tab 4 a shows all minor and moderate symptoms that were observed at least two times, Tab 4 b lists minor symptoms occuring only once.

Table 4 b: Minor Symptoms Observed Only Once After Pesticide Exposure in Children (GIZ-Nord, 1996 - 2000, cases described in Tab. 3 are excluded)

Insecticides	
Carbamates	frequent belching
chlorinated hydrocarbons	atopic dermatitis
alkyl phosphates	sore throat, thirst, irregular taste perceptions, slightly elevated liver enzymes, change of hair consistency
pyrethroids	(slight) dyspnoe, discoloration of feces, paleness
others or unknown	refusal of drinking
Herbicides	detachment of skin (1 finger), respiratory sound, urticaria
Fungicides	disturbed perception, cardiac sound
Wood protection products	asthmatic attack (minor), edema (small area of arm)

Frequently - in 42 % of all cases - patients suffered from gastrointestinal irritation after exposure to pesticides, especially to rodenticides and insecticides. With lower frequency fever and dermal irritations are reported. Other symptoms occured in less than 10 % of all symptomatic patients; higher frequencies of these symptoms are not observed if selected pesticide groups or subgroups were analysed.

Discussion:

The data analysis shows that inquiries to the poison centre on pesticide exposures in childhood are rare events in Northern Germany. This is different in other parts of the world, especially in developing countries. Clinical symptoms during or after exposure to pesticides seldom occur in these pediatric patients. In most documented cases symptoms were minor. The reason for this is not systematically analysed yet, but obviously the absorbed doses were low in the majority of the cases analysed.

Table 4 a: Frequency of Symptoms Observed More Than Once After Pesticide Exposures in Children (GIZ-Nord, 1996 - 2000)

	general weakness	fever	any bleeding	mild dermal irritation	mild irritation of eye	mild irritation of airways, cloughing	tachycaridia	hypersalivation	any symptom of GI irritation	*nausea*	*vomitting*	*bowel pain*	*diarrhea*	sedation	sleep disorder or hyperactivity	seizure	tremor	ataxia	mydriasis or miosis	headache	vertigo	paresthesia / anesthesia	others	N° patients
insecticides	1	11	3	7	5	5	2	3	36	*3*	*23*	*8*	*11*	4	5		2	2	2	2		3	11	**85**
alkyl phosphates		*5*	*2*	*4*	*3*		*1*	*1*	*13*	*1*	*5*	*7*	*5*	*2*	*1*			*1*	*1*	*1*		*1*	*5*	***37***
pyrethroids	*1*	*1*			*2*	*2*		*1*	*8*	*1*	*6*		*2*	*1*	*2*			*1*	*1*	*1*		*1*	*3*	***19***
chlorinated CH		*2*		*1*		*1*			*2*		*1*		*2*										*1*	***6***
carbamates							*1*		*2*	*1*	*1*			*1*	*1*		*1*						*1*	***4***
others or unknown		*3*	*1*	*2*		*2*		*1*	*11*		*10*	*1*	*2*		*1*		*1*					*1*	*1*	***19***
rodenticides		6	2	3					18	*4*	*12*	*4*	*4*	1	3	2				2			2	**32**
anticoagulants		*3*	*1*	*1*					*5*	*1*	*3*	*2*	*1*	*1*	*1*	*1*				*2*				***11***
phosphides				*1*					*4*	*1*	*1*	*2*	*1*		*1*									***4***
others or unknown		*3*	*1*	*1*					9	*2*	*8*		*2*		*1*	*1*							*2*	***17***
repellents				2	2				4	*1*	*1*	*2*	*1*	1								1		**10**
herbicides	1	3		6		1			7	*1*	*6*	*3*								1		1	3	**20**
fungicides		3		2	3	2			3	*1*	*3*			1	1						1	2	2	**12**
molluscicides				2		2		2	3		*3*			1					1					**7**
wood protection prod.					1	3			3		*2*		*1*		1	1					1		2	**10**
total	**2**	**23**	**5**	**22**	**11**	**13**	**2**	**5**	**74**	***10***	***50***	***17***	***17***	**8**	**10**	**3**	**2**	**2**	**3**	**5**	**2**	**7**	**18**	**176**

All symptoms described may have different causes and are not specific effects leading conclusively to one xenobiotic. Furthermore, in many cases (including all cases evaluated as "moderate") the effects reported after exposure are different from effects known from descriptions of adult poisoning cases or experimental animal toxicology with the suspected substances.

For the majority of the cases this may indicate that the symptoms were not caused by the exposure described. For some substances, however, these observations may help to recognise toxic effects of pesticides not described earlier. Compilation of data from other sources, e.g. other poison centres (possible when similar database structures are used), and continuation of data collection in the future may often help to differentiate between these two alternative meanings.

References:

1. Annex II to EU council resolution 90/C329/03 (24-11-1995)

2. Hahn A, Wolski M, Noack K, Heinemeyer G, Kayser D (1994) Erfassung der Vergiftungsfälle und Auswertungen in den Informations- und Behandlungszentren für Vergiftungen in der Bundesrepublik Deutschland. Berlin: Max von Pettenkofer-Institut des Bundesgesundheitsamtes (MvP-Hefte 5/1994)

3. Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino.J (1998) Poisoning Severity Score. Grading of Acute Poisoning. Clin. Toxicol. 36, 205-213

Open Presentation

II.3.4. Toxic exposures to pesticides in children under 15 years: a one year experience of the north of france poison centre

Open Presentation

Monique Mathieu-Nolf, V. Dherbecourt, O. Aron, D. Peucelle, P. Nisse

There is a growing number and availability of pesticides used for agriculture, gardening, household, therapeutics and food. Therefore children may be exposed frequently but few data are available to support concerns about pesticides exposures among children in developed countries.

Objectives

In order to investigate if pesticides exposures are resulting in health effects in children. All pesticides toxic exposure cases of children younger than 15 years reported during 2000 to both the Toxicovigilance Unit and the Poison Information Unit of the Lille Regional Poison Centre were reviewed. All records were evaluated for the following data elements: age, gender, circumstances, type of pesticides described by the IPCS classification of use chemical class and medical outcome. The medical outcome severity was scored using the Poison Severity Score (P.S.S.) (1) evaluated at the end of follow up.

Results

In 2000, out of 14188 cases of toxic exposures of children younger than 15 years reported, 423 (3%) were related to pesticides. Age ranged from 3 months to 13 years with a mean age of 2.70 years $\pm$ 2.04 years. The distribution by group of age shows (table I) that the large majority (89%) were younger than 5 years

Age (years)	Number of cases	%
< 1	28	7
1 - 4	347	82
5 - 9	40	9
10 - 14	8	2

Table 1: Distribution by group of age

The circumstances were accidental in all cases including home accident (97%), outdoor air pollution (1%), food (1%), accidental misuse (1%). No case related to occupational activity was reported. The route of exposure was oral (85%), dermal (6%), inhalation (4%), ocular (4%) and nasal (1%).

The pesticides involved were classified according to IPCS pesticides classification as:

- pesticides for use against plants in 8%, including herbicides (86%) and algicides (14%),
- pesticides for use against animals in 89%, including insecticides (58%), rodenticides (34%), molluscicides (6%) and others (2%),
- pesticides for use against micro-organisms in 3% including, fungicides (99%) and others (1%).

The main chemical classes of substances involved were anti-vitamine K (26%), hydrocarbons (16%), pyrethroids (17%), glucochloral (15%), organophosphates (12%), carbamate (8%), glyphosate (3%), organochlorined compounds (1%).

The severity of health effects resulting of pesticides toxic exposures was : no effect (PSS = 0) in 78%, mild severity (PSS = 1) in 21%, moderate severity (PSS = 2) in 1%. No case with high severity (PSS = 3) nor death (PSS = 4) was observed and all cases recovered without sequelae. The table II shows the distribution of cases by use class of pesticide and severity and that the most severe cases were related with pesticides against animals (1 insecticide, 2 rodenticides, 1 molluscicide, 1 nematicide).

Table 2: Number of children by use class of pesticides and severity

Pesticides use class	**Severity**			**TOTAL**
	PSS = 0 No	**PSS = 1 Mild**	**PSS = 2 Moderate**	
Pesticides against plants	**22**	**13**	-	**35**
herbicides	20	10	-	30
algicides	2	3	-	5
Pesticides against animals	**300**	**72**	**4**	**376**
insecticides	164	55	1	220
rodenticides	116	11	2	129
molluscicides	19	5	-	24
others	1	1	1(nematicide)	3
Pesticides against micro-organisms	**9**	**3**	-	**12**
fungicides	7	3	-	10
others	2	-	-	2
Total	331	88	4	423
%	78%	21%	1%	100%

This one year study in a Regional Poison Centre shows that :

- young children living in their house are exposed to numerous pesticides use against plants, animals or micro-organisms by several routes including oral, dermal, inhalation,
- the health effects resulting from acute exposure to pesticides among children were not very frequent (3%),
- the majority of cases were not severe with 21% of mild and 1% of moderate severity,
- the frequency of severe case after pesticides toxic exposure is comparable in children (1%) and adults (0,6%),
- the most severe cases in children were related to exposure to pesticide against animals,
- only acute and subacute exposure were reported to the Poison Information Unit or to the Toxicovigilance Unit and this raises the question of the identification and report of

illness among children resulting of chronic exposure to pesticides by health professionals.

There is a need of surveillance in order to evaluate the health effects resulting from acute, subacute and chronic exposures to pesticides in children and health care professionals should be reminded to consider environmental exposures of children to pesticides.

References:

1. Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino.J (1998) Poisoning Severity Score. Grading of Acute Poisoning. Clin. Toxicol. 36, 205-213

Open Presentation

II.3.5. A review of the effects of low-level exposure to OP pesticides in children

Open Presentation

Joanne Hughes, Alex Capleton, Carol Courage, Simon Short, Len Levy

Introduction

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 on organophosphates to take forward research recommendations from the DH's Committee on Toxicity and other 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 (OP) 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, and is due to be completed in April 2002.

Health effects in children (and adults) following low-level exposure to OPs in the womb, or during childhood

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, with particular attention being given to investigating whether there is a class effect. Human findings, because of their paucity, 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.

Although it was anticipated that the available data would be limited, it has not been possible to locate any studies that directly address the issue at hand. The latency of health effects that develop as a result of long-term, low-level exposures makes them difficult to study. Many studies do not have a sufficient follow-up period to allow detection of health effects that become apparent only after many years of exposure, or develop many years after a critical period of exposure. In addition, they are often not powerful enough to detect subtle changes, such as behavioural effects. The numerous epidemiological studies that attempt to addess whether pesticides cause ill-health in humans, including children, have problems, usually confounding or poor exposure assessment and characterisation. Thus they cannot be confidently used in relation to OPs and children for the effects of low-level exposure.

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*Copies of workshop proceedings available at: www.doh.gov.uk/opwkshop.htm

It is plausible that the foetus and child might be more susceptible to the effects of OPs, in particular effects relating to behaviour are most commonly hypothesised. There are experimental animal studies which have found that OPs interact with certain brain proteins involved in key stages of brain development, thus there is a potential for development to be affected. Unfortunately, these studies use doses that cannot be extrapolated to low doses in humans. It is well established that, following low doses of OPs, the levels of acetylcholinesterase in young animals recover quicker than adults, and the reverse is true for high doses. Therefore it is not possible to extrapolate the effects of OPs on brain development from high doses to lower doses.

It is clear from the published literature that OPs have the potential to affect development in experimental animals, but that this has not been investigated in humans.

Exposure of the foetus and infants to OPs in the UK

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 primary sources of foetal and infant exposure to OPs in the UK are potentially pre-natal exposure, dietary exposure, exposure from use of products containing OPs in the residential environment, para-occupational exposure and occasional other environmental exposures (e.g. hospitals, aircraft, etc.). Only one study in the US has looked at pre-natal exposure, and suggests potential foetal exposure to OP metabolites, however, interpretation of the results is difficult. Available evidence on dietary exposure indicates that drinking water, human milk, infant milk formulae and infant foods contain no or very low levels of OPs. Adult foods do contain higher levels of OPs, but still at low levels. There are currently no UK data on other sources of exposure to OPs. In particular, there is an absence of data on the usage of OP products in the residential environment. However, studies in the US and other European countries indicate that younger children, children living in urban or agricultural areas, or those whose parents are professional pesticide applicators may receive higher exposure to OPs than control groups.

Acknowledgement

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The views expressed here are those of the authors.

Open Presentation

II.4. Estimation of exposure by modeling and/or measuring

II.4.1. Modeling exposures to pesticides: Approaches and modeling needs

Open Presentation

Halûk Özkaynak, Valerie Zartarian, Jianping Xue, Ed Furtaw and Marc Rigas

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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Open Presentation

II.4.2. Requirements for models used for exposure assessment to pesticides

Open Presentation

Leah Rosenheck, presented by Curt Lunchick

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 Northlh Amercia are the SHEDS model developed by EPA's Office of Research and Development, Calendex developed by Novigen Sciences, Inc., CARES/RExY developed by Infoscientific.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.

Open Presentation

II.4.3. Deterministic versus probabilistic estimation of exposure?

Olaf Mosbach-Schulz

Both deterministic and probabilistic exposure modeling start with the identification of model structure and exposure pathways. The model assumptions should be appropriate with regard to the objectives of the analysis. This means that all input and output variables are compatible among one another, have the appropriate level of aggregation (with respect to the spatial and temporal scales), a corresponding resolution limit and are convenient to those models, which are linked to the analysis. Also the theoretical background of the model should be accepted by the community of users. The data should be representative for the population of interest and of appropriate sample size to estimate a central tendency and upper quantiles of the distribution. Here is no difference between these two kinds of modeling.

Guidelines for probabilistic modeling often include a deterministic approach as first step of the analysis. The reason is the simplicity of calculation. It requires less time and effort to start with a deterministic model. Taking estimates of the central tendency as input values gives a vague estimate of the expected exposure, which can be easily understood and communicated. “Worst case”-assumptions will turn out an upper value of exposure, which protects the human health, when it is below the limits of intervention.

Summing up, it may be said that deterministic modeling is an consistent approach, based on standard equations and exposure assumptions, which carries on the historical practice.

What are the disadvantages of the deterministic analysis? Also in simple cases the deterministic approach computes incorrect predictions of the mean and upper quantiles.

Model:	N	→	exp(N)
Deterministic:	Central tendency: 0	→	1
Probabilistic:	Standard-normal distribution N(0,1) with mean: 0	→	Log-normal distribution with mean: 1.64

Model:	U_1, U_2	→	$U_1 + U_2$
Deterministic:	Upper 95%-quantiles: 0.95, 0.95	→	1.90
Probabilistic:	Independent uniform distribution on (0,1); with upper 95%-quantiles: 0.95, 0.95	→	Triangular distribution with 95%-quantile: 1.68

The single point estimator of exposure has no interpretation in terms of the underlying distribution of the population. It provides only a little insight into the range of risks and doesn’t control the part of the population, which is protected by the estimate.

There are many reasons to incorporate stochasticity into the modeling. Regulatory authorities are especially interested on extreme events. This will be modeled by the distribution of exposure, especially the upper tails. Furthermore characterise a probabilistic model both the variation of exposure amongst the individuals in the population and the uncertainty of the underlying prediction. Model analysis turns out important pathways and input variables and final better understanding of the stochastic nature and the limitations of understanding.

How much stochasticity is required for this purpose? Also in deterministic models this question arise. To avoid extreme estimates of exposure often only a few number of input variables were set to their worst case assumptions, while the others were taken as mean values.

This distinction between important and unimportant variables can be formalised by screening procedures. Here the model will be simplified by local or global linear approximations and only rough information on location and variation of the input terms are needed to calculate some quantitative measures of importance.

Sensitivity measures		
Reduction of complexity:	Local strategies:	Global strategies:
Linearisation	Gauss error propagation	Multiple regression
Reduction of dimension	Conditional distribution	Correlation coefficient
Stepwise procedures	Stepwise variance	Stepwise regression

Variables, which contribute only a little to the output and its overall variability or uncertainty, can be described from a fair database with simple distributions. The simplest form is a one-point distribution, that means a deterministic value for the central tendency.

The probabilistic approach can be restricted to significant pathways and parameters. These are important variables, which influence the overall variation very strongly and have to be described more exactly.

Only at this point the probabilistic model needs additional investigations. A rough assumption, as a single point estimate, will lead to uncontrolled results. And a deterministic model should be revised at this point, when further information are available.

The key questions to select the right family of distributions for a input variable in a probabilistic model are: Is there a mechanistic basis for choosing a distributional family? Is the variable discrete or continuous? What are the bounds? Is the distribution skewed or symmetric? What other aspects of the shape of the distribution are known? And depending on the choice statistical estimation procedures will carry out the best fitted distribution to the empirical data. But also expert judgement can help to find the right choice.

Modern computer software enable us to simulate complex probabilistic models in moderate time. Visualisation of the results provides more information on variability and uncertainty to the decision maker and give the chance to communicate the range of risk in the population and quantitative confidence limits to the estimates.

A final sensitivity analysis identifies the drivers of risk and exposure in a quantitative form, like the screening procedure from the start. That leads to subpopulations with high risk and extreme individual exposure scenarios.

So the probabilistic risk assessment is an expansion to the deterministic modeling and is not in contradiction with it. Probabilistic modeling requires further investment of time and resources, especially the extensive use of statistics, but it turns out more information and a better understanding of the exposure scenario. This is the right way to take up the challenges of complex risk management decisions.

References:

1. Burmaster, D.E. & Anderson, P.D. (1994): *Principles of Good Practice for the Use of Monte Carlo Techniques in Human Health and Ecological Risk Assessments.* Risk Analysis 14 (1994) 477-481.
2. Morgan, M.G. & Henrion, M. (1990): Uncertainty: a Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis. University Press, Cambridge.
3. Mosbach-Schulz, O. (1999): Methodische Aspekte probabilistischer Modellierung. UWSF – Z. Umweltchem. Ökotox **11** (1999)
4. Mosbach-Schulz, O. (2000): Darstellung von Sensitivitätsmaßen in Probabilistischen Modellen an Hand der Expositionsmodellierung des QRA-Berichtes VII. Universität Bremen: Gutachten, 2000.
5. U.S. Environmental Protection Agency (EPA) (1997): *Risk Assessment Forum: Guiding Principles for Monte Carlo Analysis.* Washington: EPA/630/R-97/001, March 1997.
6. U.S. Environmental Protection Agency (EPA) (1999): Risk Assessment Guidance for Superfund: Vol.3 Part A, Process for Conducting Probabilistic Risk Assessment. Washington: Draft, December 1999.

II.4.4. Uncertainty and variability of exposure data

Open Presentation

Odile Mekel

Exposure assessment can involve a broad array of information sources and analysis techniques. Even if actual exposure-related measurements exist, assumptions or deductions will still be required because data are not likely to be available for all aspects of the exposure assessment. Moreover, the available data may be of questionable or unknown quality.

In common use, the term "uncertainty" in a exposure estimate can be viewed as composed of variability as well as true uncertainty.

Variability arises from true heterogeneity across people, places or time. Variability in exposure is related to an individual's location, activity, and behavior or preferences at a particular point in time, as well as pollutant emission rates and physical/chemical processes that affect concentrations in various media (e.g., air, soil, food and water). For example, different children in a population ingest different amounts of tap water each day. This water may contain different concentrations of chemical substances. Thus, variability is a fundamental property of the exposed population.

Uncertainty represents a lack of knowledge about factors affecting exposure. For example, although we may not know much about the issue now, we may learn more about certain people's ingestion of home-grown vegetables through suitable measurements or questionnaires. In contrast, through measurements today, we cannot now eliminate our uncertainty about the number of children who will play on a playground in a new residential area scheduled for construction in 2015. Thus, uncertainty is a property of the analyst performing the exposure assessment.

Uncertainty may be reduced by further measurement or study whereas variability cannot be reduced by further study.

Another reason for differentiating between uncertainty and variability relates to the implication for decision-making. Uncertainty may force decision-makers to judge how probable it is that exposures have been overestimated or underestimated for every member of the exposed population, whereas variability forces them to cope with the certainty that different individuals are subject to exposures both above and below any of the exposure levels chosen as a reference point (EPA, 1997).

At a more fundamental level, three types of variability can be distinguished (Table 1):

• Variability over time (Temporal Variability);

• Variability across locations (Spatial Variability);

• Variability among individuals (Inter-individual Variability).

Table 1 Categories of variability with examples (EPA, 1997)

Category	Examples
Time	• long-term: seasonal fluctuations in weather, food consumption, pollutant level, pesticide applications, fraction of time spent outdoors • short-term: industrial or personal activities on weekdays vs. weekends or at different times of the day
Space	• pollutant levels (urban vs. rural area), regional differences in food consumption (e.g. fish)
Population	• human characteristics: age, bodyweight • human behaviours: location, activity patterns

The problem of uncertainty in exposure or risk assessment is relatively large, and can quickly become too complex for facile treatment unless it is divided into smaller and more manageable topics. One method of division involves classifying sources of uncertainty according to the step in the risk assessment process (hazard identification, dose-response assessment, exposure assessment or risk characterization) at which they can occur.

The U.S. EPA (1992) has classified uncertainty in exposure assessment into three broad categories:

1. Uncertainty regarding missing or incomplete information needed to fully define exposure and dose (Scenario Uncertainty).
2. Uncertainty regarding some parameter (Parameter Uncertainty).
3. Uncertainty regarding gaps in scientific theory required to make predictions on the basis of assessment; causal inferences (Model Uncertainty).

Identification of the sources of uncertainty in an exposure assessment is the first step in determining how to reduce that uncertainty. The types of uncertainty listed above can be further defined by examining their principal causes (table 2).

Table 2 Sources and examples for types of uncertainty (EPA, 1997).

Type of uncertainty	Sources	Examples
Scenario uncertainty	Descriptive errors	Incorrect or insufficient information
	Aggregation errors	Spatial or temporal approximations
	Judgment errors	Selection of an incorrect model
	Incomplete analysis	Overlooking an important pathway
Parameter uncertainty	Measurement errors	Imprecise or biased measurements
	Sampling errors	Small or unrepresentative samples
	Variability	In time, space, or activities
	Surrogate data	Structurally-related chemicals
Model uncertainty	Relationship errors	Incorrect inferences on the basis for correlations
	Modeling errors	Excluding relevant variables

Traditionally, exposure and risk assessments have been conducted using a point estimate approach in the exposure and risk model. In the point estimate approach, a single value is assigned to each variate in the model (e.g., drinking water intake is assumed to be 2 L/day). The point estimates chosen often represent upper-end values for the variate (worst case approach). The outcomes of a point estimate model are single estimates of exposure. They are generally near the high-end of the range of estimated exposures and are therefore protective of public health. However, the single point estimate approach provides only limited information on the variability and uncertainty in the dose or risk estimates. In probabilistic analysis variability and uncertainty in exposure modeling can be treated quantitative or semi-quantitative and may lead to an increase in information on which to base decisions.

Using the example of residential living on a contaminated site, a probabilistic exposure assessment is performed, with variability and uncertainty being modeled separately. Equation 1 is used to model the average daily dose for children due to ingestion of contaminated soil.

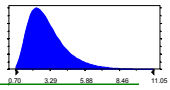
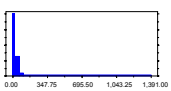
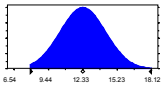
Equation 1

$$ADD_s = \frac{IR_s \times C_s}{BW}$$

ADD_s = Average Daily Dose $(ng/(kg \bullet d))$
IR_s = Soil Intake Rate (mg/d)
C_s = Soil Concentrat ion (mg/kg)
BW = Body Weight (kg)

In the conventional deterministic approach of exposure modeling, we use point estimates for each input parameter (IR_s, C_s, BW; see Table 3). In the worst-case-approach, we use highly conservative assumptions e.g. high rate of soil ingestion, upper value for the concentration in soil and a low bodyweight. Worst-case scenarios are used in order to be virtually certain that potential exposures and health risks will not be underestimated. The calculation leads to a single value estimate of the average daily dose (ADD).

Table 3 Quantification of the input parameters

	Point estimate worst-case	Probability Density Function
Concentration in soil (C_S) (mg/kg)	6.2	Lognorm: μ= 3.1 σ= 1.5 
Soil Intake Rate (IR_S) (mg/d)	100	Cumul: ≤ 10% = 0 50% = 16 90% = 67 95% = 110 Max.= 1391 
Body Weight (BW) (kg)	7.9	Tnorm: μ= 12.33 σ= 1.93 

In the probabilistic approach, each input parameter is characterized by a probability density distribution, which characterizes the variability of the input parameter. Using computer simulation, the ADD can be estimated as a distribution, too. In the example, for each model parameter such distributions were taken, making use of the recommendations in literature (Table 3). Using the computer programm @RISK, we calculated the following distribution for the theoretical daily dose for children (Figure 1A).

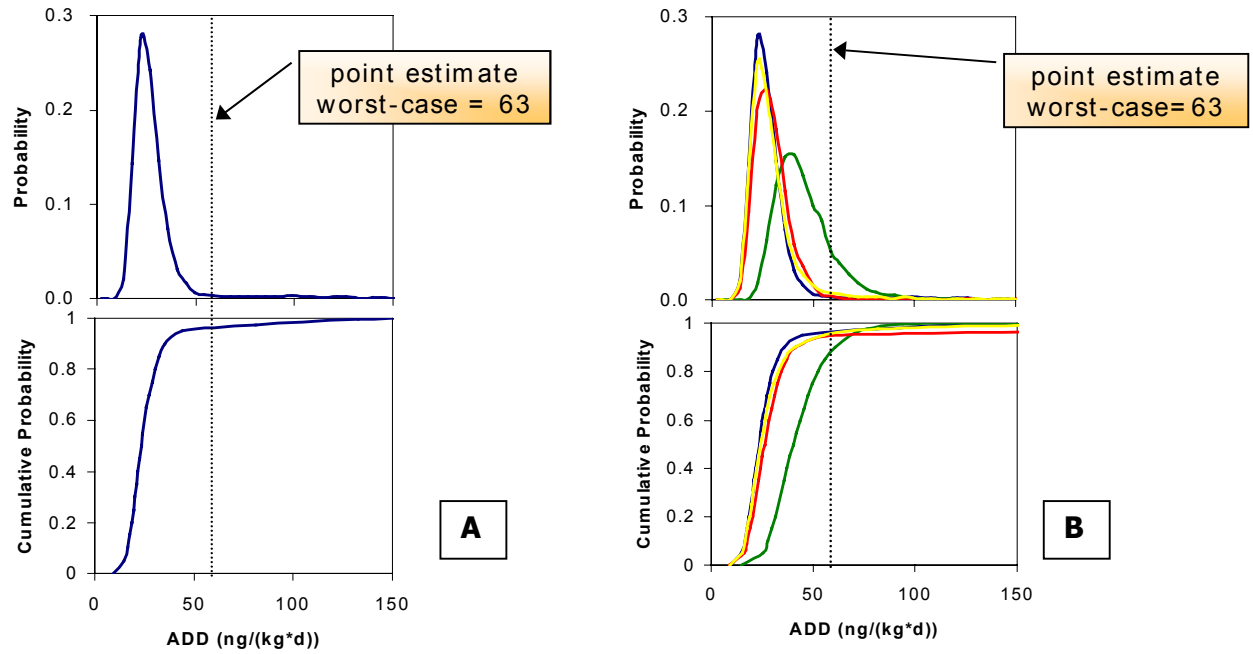
As soil intake rate by children is an exposure variate which is associated with various uncertainties about the variability, we modeled this uncertainty, making use of distributions recommended by different working groups for this exposure variate (Table 4).

Table 4 Modeling uncertainty concerning soil ingestion

Author	Distribution	Distribution parameters
Finley et al. 1994	Empiric (cumulative)	≤ 10% = 0 90% = 67 50% = 16 95% = 110 Max.= 1391
Lin, 1994	Lognormal	μ= 250 σ= 130
Stanek & Calabrese, 1995a	Empiric (cumulative)	25% = 10 90% = 186 50% = 45 95% = 208 75% = 88 Max.= 7703
Stanek & Calabrese, 1995b	Lognormal	μ= 104 σ= 758

If we model these in the same way as before, we obtain the curves for the ADD in Figure 1B. From this distributions we can derive specific moments of interest like median or specific percentiles and tabulate them.

Figure 1 Dose estimation accounting for variation (A) and uncertainty (B)



Conclusions

- In the example, the estimates for the exposure covered a range from 8.9 - 9800 ng/(kg*d)
- Uncertainty: For the 4 distributions, the medians of the exposure estimates were similar, but higher percentiles differed strongly, e.g.:

  97.5 percentile: 77 - 331 ng/(kg*d)

  99.5 percentile: 120 - 750 ng/(kg*d)

  Conventional point estimates do not reveal this important pattern.

- Since the probabilistic approach makes much better use of the information at hand, we hold it to be strongly preferred to traditional "point" estimates.
- Due to the unfamiliar format of result, however, risk communication may (initially) be a harder task.

References:

1. AUH (Ausschuß für Umwelthygiene) (1995): Standards zur Expositionsabschätzung. Behörde für Arbeit, Gesundheit und Soziales (ed.), Hamburg.
2. EPA (Environmental Protection Agency) (1992): Guidelines for exposure assessment. Office of Research and Development, Office of Health and Environmental Assessment. EPA/600/2-92/001, Washington, D.C.
3. EPA (Environmental Protection Agency) (1997): Exposure factors handbook. Office of Research and Development, National Center for Environmental Assessment. EPA/600/P-95/002Fa, August 1997, Washington, D.C.
4. Finley, B., Proctor, D., Scott, P. et al. (1994): Recommended distributions for exposure factors frequently used in health risk assessment. Risk Analysis 14: 533-553.
5. Lin, Y. (1994): Simulationsmodell zur Cadmium-Exposition durch Altlasten vor und nach der Sanierung. VDI-Fortschrittberichte Reihe 15: Umwelttechnik Nr. 130. VDI Verlag, Düsseldorf.
6. Mekel, O.C.L., Fehr, R. (2000): Berücksichtigung von Variabilität und Unsicherheit in quantitativen Risikoabschätzungen (QRA). Umweltwissenschaften und Schadstoff-Forschung 12 (1): 42 - 50.
7. Palisade Corporation (1996): @RISK. Risk Analysis and Simulation Add-In for Microsoft® Excel or Lotus® 1-2-3. Windows® Version. Release March 1996. Newfield, USA.
8. Stanek, E.J., Calabrese, E.J. (1995a): Daily estimates of soil ingestion in children. Environ. Health Persp. 103 (3): 276 – 285.
9. Stanek, E.J., Calabrese, E.J. (1995b): Soil ingestion rates for use in site evaluations based on the best tracer method. Human Ecol. Risk Assess. 1(2): 133 – 156.

Open Presentation

II.5. Posters addressing different items

II.5.1. Exposure of children to creosote from wood impregnation on playgrounds

Andrea Boehncke, Inge Mangelsdorf

Creosote (coal tar) is a complex mixture of high-boiling compounds which arise during the distillation of coal. Main constituents of creosote are polycylic 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. bodyweight, skin surface of children) combined with probabilistic methods is therefore of special interest also with regard to cumulative risk assessment.

II.5.2. Homes with wool carpets, treated with permethrin - Exposure of adults and children

Edith Berger-Preiß, K. Levsen, Gabriele Leng, H. Idel, U. Ranft

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 pyrethoids 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/m³. 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 children 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 (χ^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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II.5.3. German environmental survey 1990/92 (GerES II) and 1998 GerES III): PCP in urine of the German population - spatial and temporal difference.

Christiane Schulz, Kerstin Becker, Susanne Kaus, Christian Krause, Margarethe Seiwert, Bernd Seifert

The German Environmental Surveys (GerES) are an integral part of an Environment and Health Surveillance System which includes measuring, analysing and documenting changes in the environment and in environmental health. The German Environmental Survey (GerES), which is conducted in cooperation with the German Health Survey, is a large-scale representative population study which has repeatedly been carried out in Germany. GerES I was conducted in 1985/86 followed by GerES IIa in 1990/91 (West-Germany) and GerES IIb in 1991/92 (East-Germany). In 1998, GerES III was conducted. GerES IV is the first survey for children and teenagers, for which in 2000 a pilot study has been started.

The general objectives of the German Environmental Survey (GerES) are: a) to generate representative data on the distribution of environmental pollutant concentrations in biological samples from the German population; b) to establish a database to derive reference values; c) to document spatial and temporal differences in population exposure; d) to get insight into the contribution of different compartments (air, water, food) to the body burden; e) to model the relative importance of exposure related determinants; and f) to generate information to develop strategies for exposure prevention and reduction.

In each GerES a cross sectional sample was selected using a two stage random procedure (Seifert et al. 2000). The approximate number of participating adults was 2700 in 1985/86 (GerES I), 2500 in 1990/91 (GerES IIa), 1700 in 1991/92 (GerES IIb) and 4800 in 1998 (GerES III). The study populations were representative for the West- and East-German population with regard to community size, age (25 to 69 years in GerES I – II and 18 to 69 years in GerES III) and gender. In GerES IIa and GerES IIb children aged 6 to 14 years who lived in the households of the adult subjects, were included.

Biomonitoring was carried out using samples of urine, blood, and scalp hair. In addition, samples of house dust, tap water and outdoor dustfall were analysed. Questionnaires were used to collect information about the characteristics of the household, the subjects' habits etc.

In GerES I - III some 3000 samples of morning urine selected randomly were analysed for their concentration of PCP and creatinine (1985/86: N = 404 adults, 1990/91: N = 1026 adults and N = 498 children; 1991/92: N = 268 adults and 197 children; 1998: N = 642 adults). PCP was analysed by gas chromatography (GC) after hydrolysis (Heinrich-Ramm et al. 1995) and creatinine according the Jaffé method.

Statistical tests (t-test or variance analysis) were carried out to detect significant differences ($p \leq 0.001$) of the geometric means of the subgroups.

The mean level of PCP in urine of the adult population aged 25 to 69 years had decreased from 1.9 µg/g creatinine in 1990/92 (GerES II) to 0.9 µg/g creatinine in 1998 (GerES III). In West-Germany, where PCP had already been determined in 1985/86 (GerES I) the level of PCP in urine of adults decreased from 3.0 µg/g creatinine in 1985/86 to 2.0 µg/g creatinine in 1990/91 and to 0.9 µg/g creatinine in 1998. This is due to the fact that in 1989 the production, the application as well as the trade and commerce of PCP and products and formulations containing PCP was forbidden (PCP-V 1989). For children studied in GerES II (1990/92) a mean level of 2.9 µg/g creatinine was found. The comparison of the PCP content in urine of adults and children showed higher levels for

children. This is due to the childrens' specific exposure-relevant behaviour patterns and their specific physiological characteristics. In contrast to the situation for adults in 1990/92 and 1998, the mean values for children obtained in GerES II were different in West- and East-Germany. West-German children had a mean PCP level of 3.2 µg/g creatinine whereas East-German children had one of 2.3 µg/g creatinine. This result is in accordance with the fact that in the former GDR wood preservatives containing PCP were rarely used in private homes compared with West-Germany.

The results can be interpreted using the Human Biomonitoring (HBM) values set by the Human Biomonitoring Commission (HBC) of the Federal Environmental Agency (Ewers et al., 1999). HBM values are derived on the basic of toxicological and epidemiological studies and thus are health-related. HBM-I is a value below which a risk of adverse health effects in the general population is not to be expected according to current knowledge. If a result exceeds the HBM-II value, there is a possibility of an increased risk of adverse health effects with the need for immediate action to reduce exposure. For concentrations in the range between HBM-I and HBM-II adverse health effects cannot be excluded with sufficient certainty. If a result falls into that range, it is recommended to verify the analytical results and to check if the high level is due to specific sources which have then to be eliminated. The HBC has defined a HBM-I value of 20 µg/g creatinine and HBM-II value of 30 µg/g creatinine for PCP in urine of the general population. Comparing the concentrations of PCP in urine as obtained in GerES II with the HBM values, it appears that 0.3 % of both children and adults had a PCP level in urine in the range between HBM-I and HBM-II and 0.2 % of both children and adults had a PCP level in urine higher than HBM-II. In 1998 (GerES III) the HBM-I value was not exceeded by any participant.

References:

1. Heinrich-Ramm R, Wieken C, Laudehr H, and Szadkowski D. (1995): Pentachlorphenol in Körperflüssigkeiten - Entwicklung eines nachweisstarken Analyseverfahrens zur Erstellung von Normwerten. In: Schiele R, Beyer B, and Petrovitch A: Arbeitsmedizinisches Kolloquium der gewerblichen Berufsgenossenschaften Wiesbaden, Germany, 159-161.
2. Ewers U, Krause C, and Wilhelm M (1999): Reference values and human biological monitoring values for environmental toxins. Int. Arch. Occup. Environ. Health 72:255-260.
3. PCP-V - Pentachlorphenolverbotsverordung (1989) BGBl. I (Bundesgesetzblatt): 2235-2236.
4. Seifert B, Becker K, Krause C, and Schulz C. (2000): The German Environmental Survey 1990/92 (GerES II): A representative population study. J. Expos. Anal. Environ. Epidemiol. 10(2):103-114.

II.5.4. German environmental survey 1998 (GerES III): Pesticides in house dust

Kerstin Becker, Margarethe Seiwert, Susanne Kaus, Christian Krause, Christine. Schulz, Bernd Seifert

The German Environmental Survey (GerES) is a large-scale population study which has repeatedly been carried out in Germany. GerES I was conducted in 1985/86 followed by GerES II in 1990/92 and GerES III in 1998. The main goal of the surveys is to analyse and document the extent, distribution and determinants of the exposure to environmental pollutants of the German general population. Field work is conducted using a combination of several tools, including questionnaires, interviews, human biomonitoring, and indoor and outdoor environmental sampling. In GerES III samples of house dust collected in homes of the study participants were, *inter alia*, analysed for their content of PCP, lindane, DDT, chlorpyrifos, propoxur and methoxychlor as well as 8 different pyrethroids and the synergist piperonyl butoxide (PBO).

The vacuum cleaner bags were taken as available in the households of the subjects. Out of 4597 samples collected 750 were randomly selected for analysis. Part of the content was sieved and the 2 mm fraction was used for analysis. Analysis was done either by GC/MS or GC/ECD depending on the extract used and the substance to be determined (Butte et al. 2001). The limit of quantification (LOQ) was 0.1 mg/kg for PCP and propoxur, and 0.05 mg/kg for lindane, DDT, clorpyrifos and methoxychlor.

Preliminary results show that the mean PCP concentration decreased from 0.32 mg/kg in 1990/92 (GerES II) to 0.25 mg/kg in 1998 (GerES III). Lindane was detected in only 24 % of the samples which resulted in a mean value below the detection limit of 0.05 mg/kg. In GerES II the mean value was 0.21 mg/kg. In GerES II mean levels of PCP in house dust were significantly higher in the Western part of the country whereas lindane mean concentrations were significantly higher in the Eastern part (Schulz et al. 1999). In GerES III the differences between the concentrations in East- and West-Germany were less marked.

DDT, propoxur, chlopyrifos and methoxychlor were found in 35 %, 8 %, 15 % and 46 % of the samples, respectively. It could be shown that in households with children significantly lower PCP, lindane and DDT concentrations were found compared to households with no children.

References:

1. Butte, W., Hoffmann, W., Hostrup, O., Schmidt, A., Walker, G.: Endokrin wirksame Substanzen im Hausstaub: Ergebnisse eines repräsentativen Monitorings. Gefahrstoffe - Reinhaltung der Luft 61 (1/2) 19-23 (2001).

2. Schulz, C., Becker, K., Friedrich, C., Krause, C., Seifert, B.: German Environmental Survey (GerES): Pesticides in the house dust of the German residential population. Prodeedings 8th Internat. Conf. Indoor Air Quality and Climate, Indoor Air 99, Edinburgh, Scotland, 1999, Vol. 2, 788-793.

II.5.5. Biocide emissions from indoor wall paints

Wolfgang Horn, Elke Roßkamp, Dieter Ullrich, Bernd Seifert

Many investigations have dealt with the emission of VOC from wall paints. While the VOC content of water-based paints has decreased over the years biocides have been added to prevent fungal growth during storage and transportation. Today, formaldehyde and a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one (CIT) and 2-methyl-4-isothiazolin-3-one (MIT) are typical preserving agents. The isothiazolinone compounds have high allergenic potential.

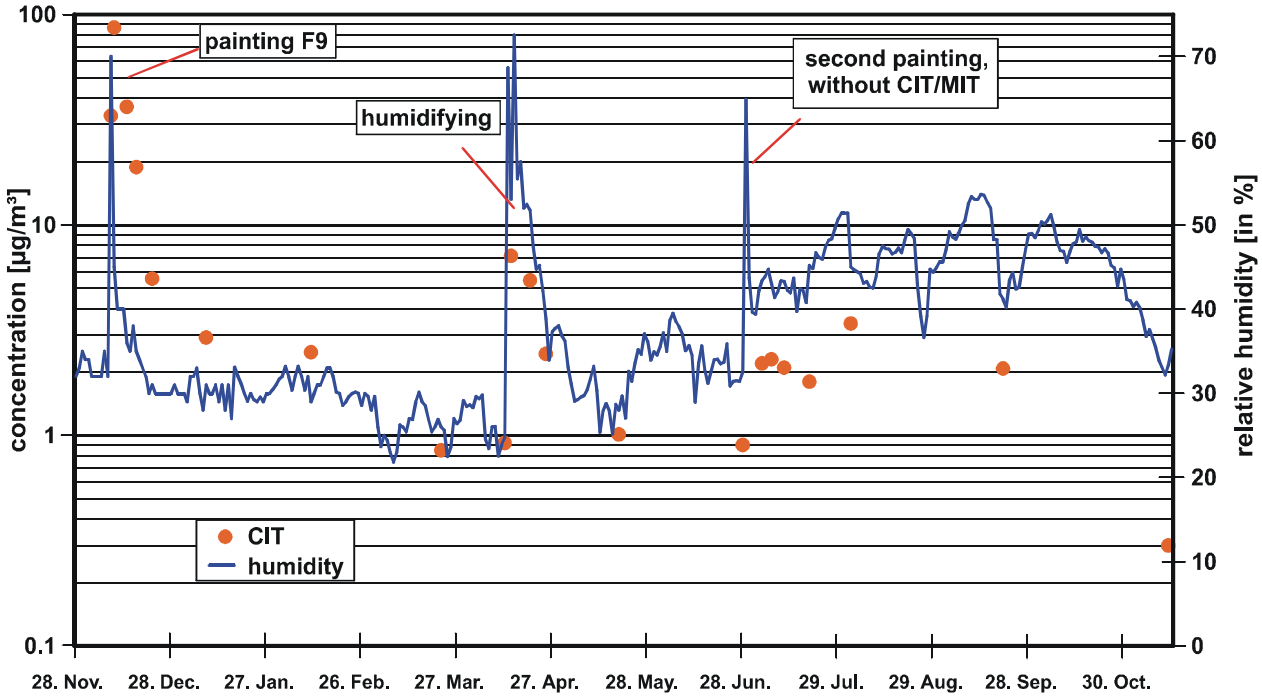
The MIT/CIT emission behaviour of 24 wall paints was studied under laboratory conditions. Sampling on TENAX TA followed by thermal desorption, gas chromatographic separation, and mass spectrometric detection (SIM mode) was used to determine the CIT/MIT concentrations. Area specific emission rates of MIT and CIT obtained in the chamber experiments were between 100 and 600 µg/m²h after 24 hours, and between 6 and 4 µg/m²h after 28 days, respectively. Additionally air concentrations in some rooms were determined after application. Two paints were applied to the walls of two test rooms. Concentrations of 25 and 85 µg/m³ after 1 day, and of < 0.12 (ld = limit of detection) and 15 µg/m³ after 1 week, and of < 0.12 (ld) and 2.5 µg/m³ after 4 weeks were obtained for MIT and CIT, respectively. Figure 1 gives an example of the influence of RH on the concentration of CIT in one test room. When, after four months, RH was increased to about 65% for 7 days the concentration of CIT increased from 1 µg/m³ to 7 µg/m³. The results show that biocides added to water-based paints for prevention of fungal growth during storage and transportation emit into indoor air and generate concentrations about 50 µg/m³ after 1 day and about 3 µg/m³ 4 weeks after application. These 3 µg/m³ concentration were used for the calculation of uptake per day for children and adults.

With ages of 1, 5,10 and 30 years values of 1, 0.8, 0.7 and 0.5 µg/d kg BW resulted (Table 1).

Table 1: Estimated exposure to CIT up to 3 months after painting, calculated with a concentration of 3 µg/m³, in different age groups.

Age		1	5	10	30
Body weight *	[kg]	9.1	18.7	33	75
Ventilation rate**	[m³/d]	3.1	4.9	7.2	12.3
Biocide exposure	[µg/d)]	9.2	14.8	14.9	36.8
	[µg/kg d]***	1.0	0.8	0.7	0.5

Figure 1: Concentration of CIT in a test room over 350 days (paint No. 9). Influence of change in relative humidity.



* Arbeitsgemeinschaft der Leitenden Medizinalbeamtinnen und –beamten der Länder: „Standards zur Expositonsabschätzung“ Behörde für Arbeit Gesundheit und Soziales (BAGS) Hamburg 1995

** Ventilation rate according to US EPA (1988) [Formel: ln MV = -0,70048 + 0,65865 ln BW (MV = ventilation in l/min, BW = Body weight in kg)]

*** Based on a resorption rate of 100%

References:

1. *Horn, W.; Roßkamp, E.; Ullrich, D. und Seifert, B.* 2000: Biocide emissions from indoor wall paints. Proceedings of Healthy Buildings 2000, Espoo, Finnland, Aug 6-10, Vol. 4, S. 397-402.
2. *Roßkamp, E.; Horn, W.; Ullrich, D. und Seifert, B.* 2001: Biozidemissionen aus Dispersionsfarben. Teil 1: Emission von Isothiazolinonen. Gefahrstoffe – Reinhaltung der Luft, **61**, S. 41-47.

II.5.6. Areas of high agricultural pesticide use in California: How many children live there?

Martha Harnly, R. Gunier, P. Reynolds, J. Von Behren and A. Hertz

ABSTRACT

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.

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.[(6)]

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

Toxicological Groups

Probable carcinogens (Class B2)[a]: 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)[b]: acephate, acrolein, amitraz, atrazine, benomyl, bifenthrin, bromacil, bromoxynil, carbaryl, chlorthal-dimethyl, cyanazine, cypermethrin, dichlobenil, dichlorvos, dicloflop-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[c]: 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[d]: 2,4-diethylamine, benomyl, bromoxynil, carbofuran, 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[e]: dicofol, endosulfan and lindane.

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

Carbamates[e]: aldicarb, benomyl, carbaryl, carbofuran, frometanate, methomyl, pebulate and propoxur.

Dithiocarbamates[e]: 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.*[(1)]

b. *Possible human carcinogens with limited evidence in laboratory animals from US EPA* [(1)]

c. *Positive in two or more laboratory assays from Gold and Zeiger* [(2)] *and US EPA.*[(3)]

d. *Positive in one or more developmental or reproductive studies in laboratory animals from CDPR.*[(4)]

e. *Chemical groups were identified from Meister.*[(5)]

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[a]

Pesticide Group	Median (lbs/mi^2)	Maximum (lbs/mi^2)	Block Groups (>1,000lbs/mi^2)	Children (<15) (>1,000lbs/mi^2)
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.[7-15] 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.[13, 17] 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.

References:

1. United States Environmental Protection Agency. Office of Pesticide Programs, Reference Dose Tracking Report. 1997.
2. Gold, Lois S.; Zeiger, Errol. Handbook of Carcinogenic Potency and Genotoxicity Databases. New York, NY: CRC Press; 1997.
3. United States Environmental Protection Agency. Genetic Activity Profile, 1997.
4. California Department of Pesticide Regulation. Summaries of Toxicology Data,Medical, Toxicology Branch, Sacramento, CA, 1997.
5. Meister, Richard T. Farm Chemicals Handbook. Willoughby, Ohio: Meister Publishing Company; 1992.
6. //www.nass.usda.gov/census/census92.
7. Majewski, Michael S.; Capel, Paul D. Pesticides in the Atmosphere. U.S. Geological Survey; Sacramento, CA, 1995. Report No.: 94-506.
8. Baker LW, Fitzell DL, Seiber JN, Parker TR, Shibamoto T, Poore MW, Longley KE, Tomlin RP, Propper R, Duncan DW. Ambient Concentrations of Pesticides in California. Environmental Science and Technology 1996;30:1365-8.
9. Hawthorne SB, Miller DJ, Louie PK, Butler RD, Mayer GG. Atmospheric Pollutants and Trace Gases. Journal of Environmental Quality 1996;25:594-600.
10. Cohen Hubal EA, Sheldon LS, Burke JM, McCurdy TR, Berry MR. Children's Exposure Assessment: A review of Factors Influencing Children's Exposure, and the Data Available to Characterize That Exposure. Environmental Health Perspectives 2000;108(6):475-86.
11. Zartarian VG, Ozkaynak H, Burke JM, Zufall MJ, Rigas ML, Furtaw EJ. A Modeling Framework for Estimating Children's Residential Exposure and Dose to Chlorpyrifos Via Dermal Residue Contact and Nondietary Ingestion. Environmental Health Perspectives 2000;108(6):505-14.
12. Quakenboss JJ, Pellizzari ED, Shubat P, Whitmore RW, Adgate JL, Thomas KW. Design strategy for assessing multi-pathway exposure for children: the Minnesota Children's Pesticide Exposure Study. Journal of Exposure Analysis and Environmental Epidemiology 2000;10:145-58.
13. Simcox NJ, Fenske RA, Wolz SA, Lee I-C, Kalman DA. Pesticides in Household Dust and Soil: Exposure Pathways for Children of Agricultural Families. Environmental Health Perspectives 1995;103(12):1126-34.
14. Bradman MA, Harnly ME, Draper W, Seidel S, Teran S, Wakeham D, Neutra R. Pesticide Exposures to Children from California's Central Valley: Results of a Pilot Study. Journal of Exposure Analysis and Environmental Epidemiology 1997;7(2):217-34.
15. Spurlock F, Burrow K, Dubrovsky N. Chlorofluorocarbon Dating of Herbicide-Containing Well Waters in Fresno and Tulare Counties, California. Journal of Environmental Quality 2000;29:474-83.
16. Loewenherz C, Fenske RA, Simcox NJ, Bellamy G, Kalman D. Biological Monitoring of Organophosphorus Pesticide Exposure among Children of Agricultural Workers in Central Washington State. Environmental Health Perspectives 1997;105(12):1344-53.
17. Fenske RA, Kissel JC, Lu C, Kalman DA, Simcox NJ. Biologically Based Pesticide Dose Estimates for Children in an Agricultural Community. Environmental Health Perspectives 2000;108(6):515-20.

II.5.7. Documentation of pesticide use in the European Union

Lars Neumeister

Within the European Union a uniform pesticide use reporting system, which delivers information on type and amount of pesticides used by commodity/crop, data and location does not exist. Most Member States collect sales data of agricultural pesticides, some maintain pesticide use surveys and in some Member States agricultural pesticide user have to keep records of their applications. The United Kingdom is the only country with a limited pesticide use reporting system, any aerial application has to be reported in detail.

Information on non-agricultural use of pesticides is not available in the EU.

In the future a uniform pesticide use reporting system should be established. Any user of a pesticide for commercial purposes should report his/her use. Minimum reporting requirements should be: date of application, amount product used, product information, location by street address and/or postal code, treated area, treated commodity/crop.

In order to establish and implement pesticide use reporting systems in the EU several actions are necessary. Firstly, legal frameworks are needed, secondly a central product label database for pesticide and biocide products needs to be built. Data harmonisation among the Member States is essential to make an efficient pesticide use reporting system work.

II.5.8. The German Food Monitoring: Models for exposure assessment of undesirable substances in food

Bettina Schmidt-Faber

The **German Food Monitoring** is an independent activity within the framework of the official food control since 1995. It provides informative data for a representative description of the occurence of undesirable substances in food and is based on a system of repeated measurements and evaluations of levels of pesticides, heavy metals and other contaminants in and on food.

Yearly about 20 different foodstuffs (of animal and plant origin) of a defined food basket are analysed for about 140 different contaminants in plant food and for about 40 different contaminants in food of animal origin (with approx. 230 samples per foodstuff). The food basket comprises about 100 different food items and reflects German food intake

- for mainly consumed foods,
- for foods consumed in great amounts and
- for foods with potentially high amounts of undesirable substances (1).

Aims of Food Monitoring:

- collection of representative data on the presence of undesirable substances in food early recognition of potential health risks from these substances
- investigation of temporal trends and regional factors
- *estimation of consumer exposure as part of risk characterization and risk management*

The **chronic dietary intake** was estimated by using monitoring data from 1995-99. The consumption figures and bodyweights are based on the German National Consumption Survey from 1988-90.

Exposure assessment was done for different population subgroups: children, adults, eaters (average daily/weekly intake) and high consumers (95. percentile of intake). The chronic intake of a contaminant was calculated by multiplying the contaminants mean concentration (2) in the specific foodstuff with its consumption (point estimation). To assess the health risk to the consumer, the actual dietary intake was compared with the toxicologically acceptable or tolerable level (ADI, the acceptable daily intake or PTWI, the provisional tolerable weekly intake).

Exemplary the results of three contaminants are presented: of the ubiquitous occurring environmental contaminant cadmium (n=15239, 64,6% quantified values), nitrate, ubiquitous in plants (n=5488, 87,2% quantified values) and of the fungicide procymidon (n=11135, 6,7% quantified values).

Since for pesticides often only in a few number of samples quantified values (often in less than 10% of all samples analyzed) are available, exemplary for procymidon, the models for exposure assessment were calculated in three different ways: A) with all values (including > 90% of zeros); B) with quantified (7%) plus non-quantifiable values (2,8%), assigned the value of 0,5 x the limit of determination and C) for quantified values only (7% of all samples).

Table1 shows the calculated percentages of ADI/ PTWI for average consumptional habits, table 2 shows some selected results for high consumers and „eaters“, in this case younger male children.

Table 1: Percentages of ADI / PTWI (average consumptional habits)

			nitrate	cadmium	procymidon
			ADI	PTWI	ADI
		bodyweight	3,65 mg	7 mg/kg	0,1 mg/kg
	n	(kg)	NO3-/kg bw	bw	bw
girl (4-10 yrs)	972	25,6	**27,2 %**	**19,3%**	**0,04% (model A)**
					0,303% (model B)
					0,201 % (Model C)
boy (4-10 yrs)	1011	26,7	**25,6%**	**20,2%**	**0,04% (model A)**
					0,299% (model B)
					0,291% (model C)
Women	10314	63,9	**18,7%**	**10,4%**	**0,03% (model A)**
					0,172% (model B)
					0,184% (model C)
Men	8934	77,8	**16,3%**	**10,8%**	**0,02% (model A)**
					0,128% (model B)
					0,131% (model C)

Table 2: Percentage of ADI / PTWI (high consumers and eaters: boys, 4-10 yrs)

			nitrate	**cadmium**	Procymidon
Potatoes	high	(159g/d)	**21,1%**	**10,2%**	-
Lettuce	high	(18,5 g/d)	**32,1%**	1,6%	0,6%
Wheat	high	(130 g/d)	**-**	**19,4%**	1,0%
spinach frozen	high	(8,3 g/d)	**7,1%**	2,3%	0,05%
	eater	(20,3 g/d)	17,4%	5,5%	0,12%
paprika	high	(18,6 g/d)	1,2%	0,5%	1,1%
Strawberries	high	(22,9 g/d)	-	0,5%	**5%**
grapes white	high	(14,3 g/d)	-	-	**15,7%**
Pear	high	(29,2 g/d)	-	0,6%	3,8%
liver (turkey)	eater	(10,5 g/d)	-	3,4%	-

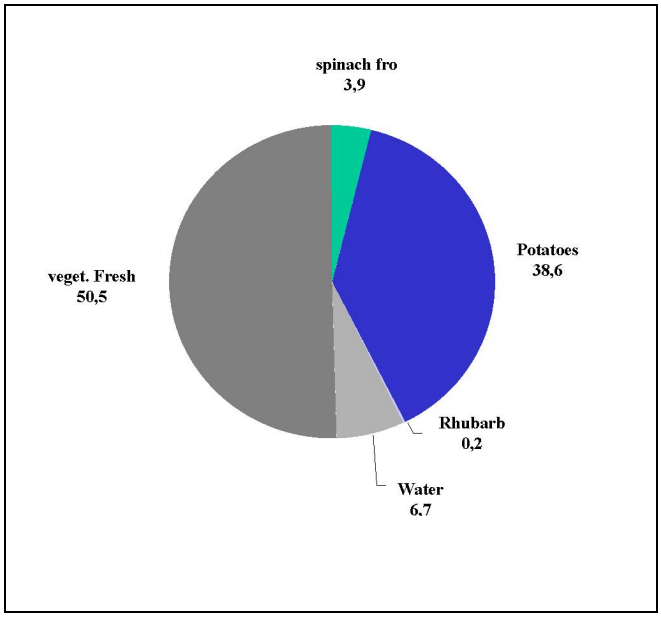


Figure 1: Contribution of food-stuffs to nitrate intake, boys

Results:

- Generally the results of monitoring show a low contaminantion of foodstuffs with undesirable substances, more than half of all analyzed samples were free of residues, only a small number of samples (<5%) exceeded guide values
- Exposure assessments show the highest utilization of ADI/PTWI for nitrate with about 30% for young girls (table 1), the comparison of the three scenarios for procymidon show differences on an 10 times scale, altogether utilization of ADI lies far below 1%
- Regarding single foodstuffs, even high consumers and eaters do not reach 50% of the ADI/PTWI (table 2)
- The number of foodstuffs with significant contribution to the intake of undesirable substances varies considerably (figures 1 to 3)

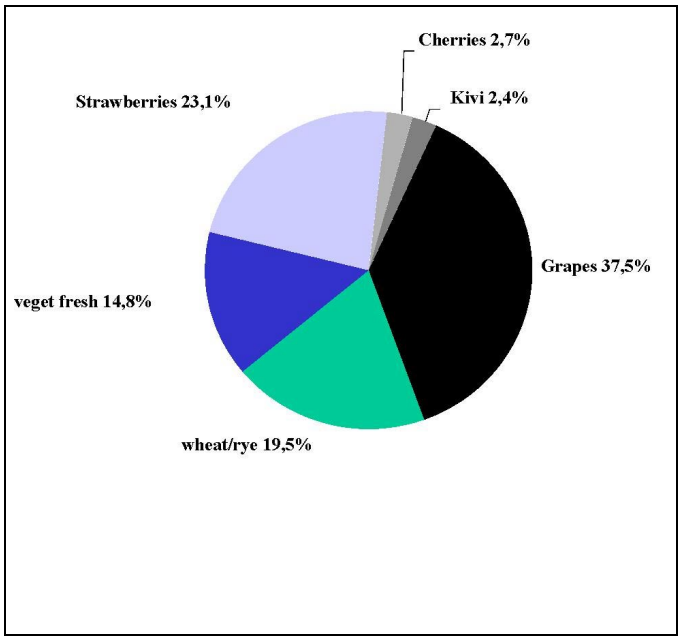


Figure 2: Contribution of food-stuffs to procymidon intake, boys

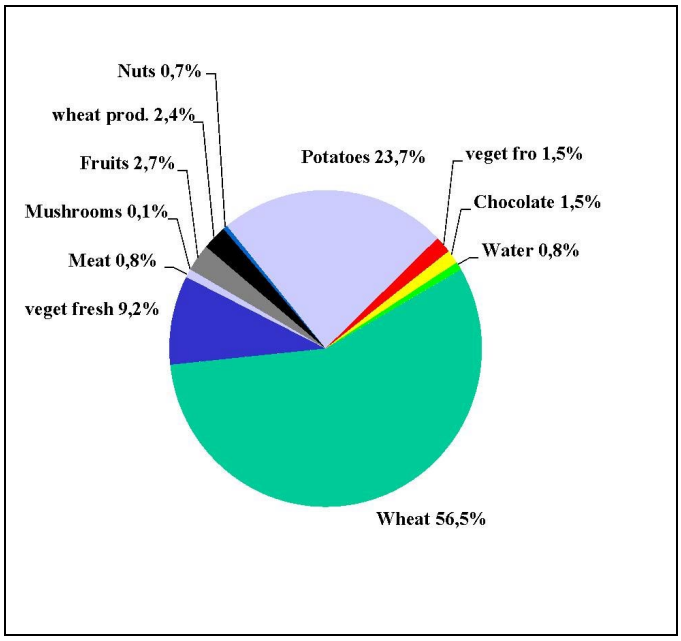


Figure 3: Contribution of food-stuffs to cadmium intake, boys

General conclusion:

Although a limited number of foodstuffs were included into the models a reasonable conclusion would be that no chronic health risks could be associated with the contaminants considered.

References

1. Schroeter et al: Warenkorb für das Lebensmittel-Monitoring in der Bundesrepublik Deutschland, Bundesgesundheitsbl 1999. 42:77-84
2. WHO/FSF/FOS/97.7 Guidelines for predicting dietary intake of pesticide residues, WHO 1997

II.5.9. Evaluation of symptoms from acute and chronic exposures of organophosphates and pyrethroids

Helga Michalak, Katrin Begemann, Gerhard Heinemeyer, Axel Hahn, Ursula Gundert-Remy

Introduction:

Pyrethroids (PY) and organophosphates (OP) are frequently used in pesticide-products. Their toxic risks are discussed widely, in particular under the aspect of low and chronic exposure.

Symptomatology of 474 cases of exposures to OP and PY containing pesticides reported to the BgVV according to chemical law have been evaluated in order to differentiate between possible acute and chronic effects.

Methods:

The analysis included 132 cases of exposure to OP and 206 cases of exposure to PY containing pesticides as well as 136 cases with combinations of OP, PY and other compounds (COMB). Symptoms and signs were examined and attributed to acute and chronic exposure. The reported symptoms were encoded according to a modified WHO-Thesaurus and a comparison of pattern of health impairment was analysed in acute exposure to OP and PY, in acute and chronic exposure to PY and in chronic exposure to PY and combinations.

Results:

Most of the 132 cases of exposure to OP were suicides (33 %), and accidents (47 %). In PY and in COMB exposures, common use was most frequent (85 and 81 %, resp.).

The suicide rate was low in PY and COMB exposures (1,5 and 4 %, resp.). On the other hand, rate of „common use“ was low in OP exposures (8 %).

In cases with exposures to OP, 16 deaths (= 3,3 % of cases) were reported, and 2 deaths (= 0,4 % of cases) after PY exposure. One case of lethal outcome was reported after exposure with a combination product.

In 15 cases no symptoms were observed, 277 showed symptoms of minor severity; 103 patients had moderate symptoms. The most severe symtomes have been observed in the OP group.

Symptomatology:

1. Comparison of symptoms after *acute exposure to OP and PY* (Fig. 1)

In cases of acute OP exposure, the analysis revealed that most of the symptoms that were observed could be attributed with typical patterns of OP-poisoning (χ^2 – Test, $p<0,05$): gastrointestinal disturbance; miosis; respiratory insufficiency; coma, convulsion, depression of consciousness; reduced Cholinesterase; cardiac shock, circulatory disturbance; fasciculations, myoclonia, tremor; bronchialsecretion excessive, hypersalivation; psychic disturbance.

In cases with acute exposure to PY headache, weakness, tiredness, disturbances of smelling, allergy have been observed. The most important symptoms, hovewer, were irritation like concerning eyes, skin, and the respiratory tract. Because these symptoms

cannot be explained by chemical irritation they can be explained as paraesthesia occuring after local absorption, which is a well documented affect of this group of substances.

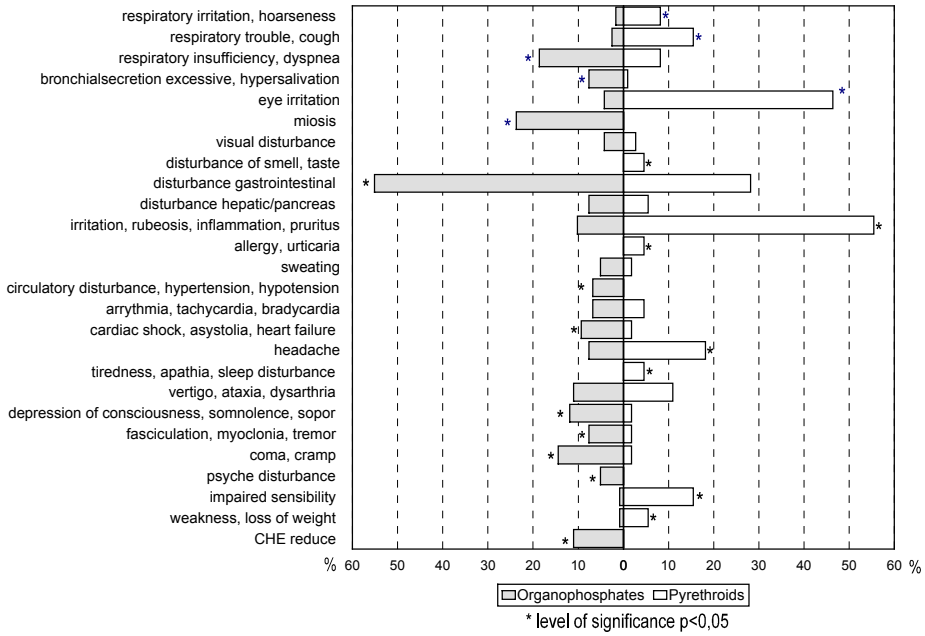


Figure 1: Comparison of symptoms after acute exposure to Organophosphates (n=118) and to Pyrethroids (n=110)

2. Comparison of symptoms after *acute and chronic exposure to PY* (Fig. 2)

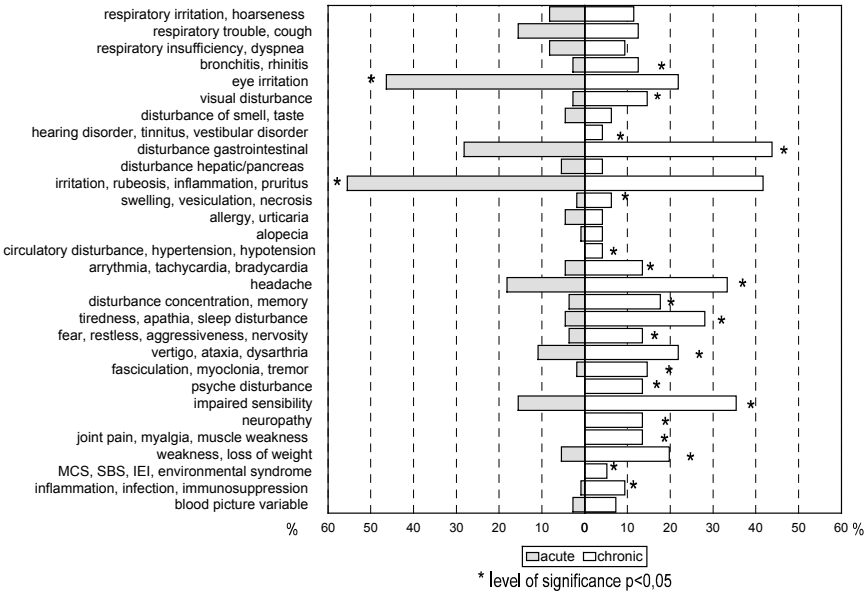


Figure 2: Comparison of symptoms after acute (n=110) and chronic (n=96) exposure to Pyrethroids

3. Comparison of symptoms after *chronic exposure to PY and Combinations* (Fig. 3)

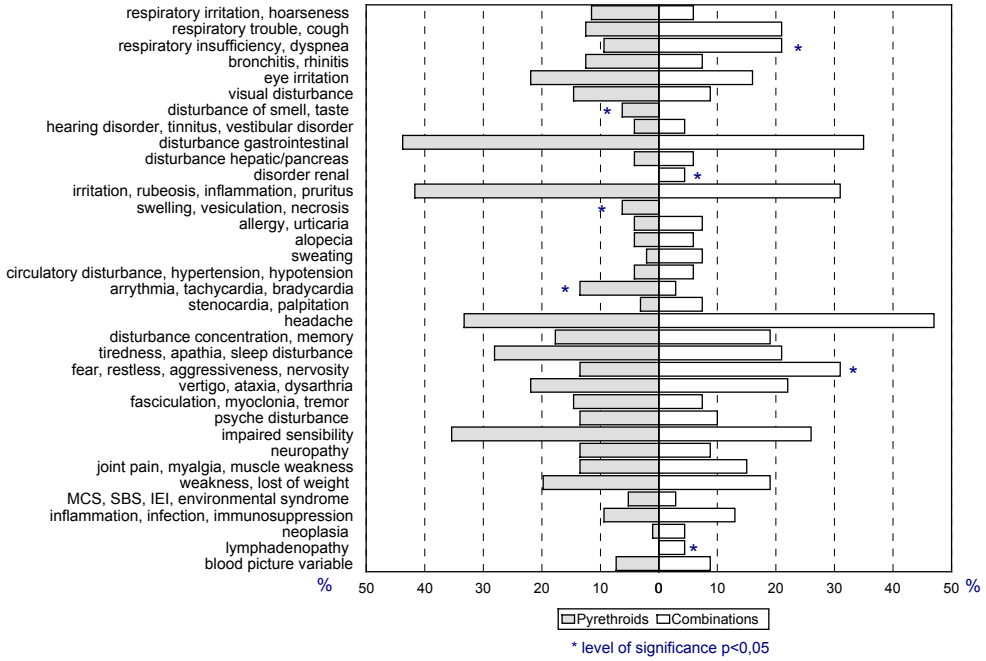


Figure 3: Comparison of symptoms after chronic exposure to Pyrethroids (n=96) and Combinations (n=68)

Interestingly, the pattern of symptoms occuring after chronic exposure to PY and combinations did not differ. This is in particular true for symptoms mentioned in the section above (figure 2).

Only few symptoms were different (χ^2 – Test, p<0,05) for chronic exposure to PY: arrythmia, disturbance of smell and taste, swelling, and for chronic exposure to COMB: fear, respiratory insufficience, renal disorder, lymphadenopathy.

Conclusion:

The differences between acute and chronic exposures to OP and PY containing pesticides as found in this evaluation points out the different modes of action:

After acute exposure, the known observed symptoms can be explained by toxic mechanism of high dose of OP. These cases can also be attributed to suicides. Acute PY-exposure may also lead to typical, but less severe effetcs. After chronic exposures, which may be associated more frequent with low amounts, the pattern of symptoms is different to that after acute exposure and may be explained by different processes.

The high number of cases with „common use“ shows, that protective measures for consumers are needed.

II.5.10. Pesticides in mother's milk

Bärbel Vieth

Introduction

Highly lipophilic pesticides with long lasting environmental and biological persistency are detectable in human milk. This is especially true for organochlorine pesticides, like DDT, hexachlorobenzene (HCB) or hexachlorocyclohexane isomers (HCH). Although their use has been banned for several decades they are detectable in the environment and in food of animal origin even today.

Food, especially animal fat, is the major source of human background exposure to organochlorine pesticides, which accumulate in human fat tissue. During the breast feeding period they pass into human milk.

Infants are exposed to organochlorine pesticides postnatally via breast feeding. Additionally prenatal exposure occurs because most of these compounds can pass the placenta. Levels in human milk are an useful measure for the body burden of the mother as well as for the prenatal and the postnatal exposure of breast-fed infants.

Concentrations on residues of persistent organochlorine pesticides in human milk samples from Germany have been analyzed for more than 20 years. The trends of these residues in human milk and the exposure of breast-fed babies are discussed.

Origin and calculation of data

Most of the human milk samples have been analyzed on request of interested mothers by the food control laboratories of the federal Länder. The data have been collected in the databank for residues in human milk and for dioxins in other human tissues established at the BgVV.

The concentrations of p,p'-DDT and its persistent metabolite p,p'-DDE are summarized as the sum of both (sum-DDT).

The calculation of the daily dietary intake by breast-fed infants has been based on the mean concentrations and the 95 percentiles, respectively, of the organochlorine pesticides in human milk samples as determined from 1997 (Table 1, 2), the mean bodyweight and the average milk intake (fat content = 3.5 %) of a 4-month-old baby.

Trends in organochlorine pesticide levels in human milk

Since 1980 about 40000 human milk samples have been analyzed for the following persistent organochlorine pesticides: dieldrin, cis-heptachlorepoxid (cis-HEPO), α-HCH, ß-HCH, γ-HCH (Lindan), HCB, p,p'-DDT and its main metabolite p,p'-DDE. These data allow reliable statements on time trends of these residues.

As a consequence of the ban of these pesticides the concentrations in human milk are declining continuously.

Levels of α- and γ-HCH, dieldrin, cis-HEPO

The levels of α- and γ-HCH, dieldrin and cis-HEPO observed in the last 10 years are in the range of or lower than the analytical detection limit. The number of samples with detectable amounts of these pesticides is between 10 and 50 %, so that the mean values calculated are strongly influenced by the detection limit.

Year	α-HCH [mg/kg fat]		γ-HCH [mg/kg fat]		Dieldrin [mg/kg fat]		cis-HEPO [mg/kg fat]	
	Mean	95 Perc	Mean	95 Perc	Mean	95 Perc	Mean	95 Perc
1979-81	0.021	0.047	0.055	0.115	0.026		0.033	0.037
1984	0.018	0.060	0.045	0.140	0.014	0.050		
1990	0.004	0.011	0.016	0.027	0.007	0.029	0.007	0.048
1995	0.004	0.012	0.016	0.050	0.008	0.024	0.007	0.020
1997	0.003	0.006	0.010	0.040	0.006	0.020	0.006	0.020

Table 1: Levels of α and γ- HCH, dieldrin and cis-HEPO in human milk from Germany

Levels of ß-HCH, HCB, sum-DDT

In almost all breast milk samples ß-HCH, HCB and DDT/DDE are detectable. The concentrations of these pesticides are higher by a factor of 10-100 than those of the pesticides described before.

During the last 20 years, the mean concentrations as well as the 95 percentiles have decreased by about 80-95%.

Year	N	ß-HCH [mg/kg fat]		HCB [mg/kg fat]		Sum-DDT [1)] [mg/kg fat]	
		Mean	95 Perc	Mean	95 Perc	Mean	95 Perc
1979-81	3390	0.327	0.903	1.075	2.098	1.831	4.033
1984	1662	0.128	0.320	0.424	1.050	1.002	2.540
1990	5316	0.077	0.164	0.218	0.523	0.551	1.323
1995	1914	0.049	0.125	0.107	0.268	0.448	1.447
1997	776	0.039	0.108	0.069	0.174	0.298	0.855
Decrease 1980-97		88%	88%	94%	92%	84%	79%

[1)] since 1991 only data of the old federal Länder included

Table 2: Levels of ß–HCH, HCB and sum-DDT in human milk from Germany

Regional differences

Since 1990 data on samples from the new federal Länder (former GDR) have also been collected. To compare the background levels of ß-HCH, HCB and DDT in human milk samples from the old and the new federal Länder the mean values are summarized in Table 3. Additionally data on samples originating from Bitterfeld, an industrial area are included.

Year	Origin	ß-HCH [mg/kg fat]	HCB [mg/kg fat]	Sum-DDT [mg/kg fat]
1990	Old federal Länder	0.077	0.218	0.551
	New federal Länder	0.080	0.170	1.250
	Bitterfeld [1)]	0.520	0.400	2.390
1997	Old federal Länder	0.040	0.070	0.314
	New federal Länder	0.068	0.083	0.872
1996	Bitterfeld [1)]	0.054	0.091	0.793

[1)] Contaminated area

Table 3: Comparison of mean values of ß-HCH, HCB and sum-DDT in human milk samples from the old and the new federal Länder

The background concentrations of ß-HCH and HCB are almost similar in the old and the new federal Länder, whereas significant regional differences of the DDT levels can be observed for 1990 as well as for 1997, resulting from the wide use of DDT in the former GDR during the eighties.

In former times technical HCH and DDT were produced or processed in Bitterfeld, a centre of chlorine chemistry. This resulted in high environmental contamination and therefore elevated residue concentrations in food produced in that region. Because of high consumption of self-produced or regional produced food in the former GDR distinctly elevated concentrations of the organochlorine pesticides in breast milk sampled in that area in 1990 are observed. However, intensive efforts for environmental reconstruction in the nineties resulted in a clear decline of the organochlorine pesticide mean levels in human milk from that region in 1997.

Current intake of organochlorine pesticides by breast-fed infants

The daily intake of organochlorine pesticides by a 4 month old fully breast-fed infant has been calculated. The mean daily intake as well as the 95 percentile are in the range of or lower than the acceptable or tolerable daily intake (ADI/TDI) derived by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Only the dietary intake of HCB exceeds the TDI value.

Pesticide	**ADI / TDI** µg/kg BW *d	**Calculated daily dietary intake**	
		Mean µg/kg BW *d	95 Percentile µg/kg BW *d
α-HCH	3	0.01	0.026
ß-HCH	3	0.18	0.49
γ-HCH	3	0.05	0.18
Dieldrin	0.1	0.026	0.09
cis-HEPO	0.5	0.02	0.09
HCB	0.16-0.17	0.31	0.75
Sum-DDT[1)]	20	1.33	3.80

[1)] only data from the old federal Länder included

Table 4: Daily dietary intake by fully breast-fed infants and the acceptable or tolerable daily intake

The ADI/TDI covers lifetime exposure of which the nursing period only constitutes a small fraction. A short- term exceedence of the ADI/TDI is not viewed as posing a health risk.

In conclusion there is no health risk for breast-fed infants recognizable. Breast-feeding is recommended by the German National Breast-feeding Committee and other expert groups.

Summary

1. Infants are exposed to organochlorine pesticides postnatally via breast-feeding and prenatally by transplacental transfer.
2. In Germany the background levels of the organochlorine pesticides (mean and 95 percentile) in human milk, i.e. the exposure of infants decreased by about 80-95 % during the last 20 years.

3. From the organochlorine pesticides analyzed in human milk from Germany, nowadays residues of ß-HCH, HCB and DDT are still detectable in relevant amounts in most of the samples.
4. The current daily intake by breast-fed babies is clearly lower than the lifetime acceptable/tolerable daily intake for most of the organochlorine pesticides.
5. The German National Breast-feeding Committee and further experts recommend breast-feeding.
6. For reasons of precautionary health protection the experts demand further efforts to reduce the levels of contaminants in human milk.

Acknowledgements:

The authors wish to thank the colleagues from the food control laboratories of the federal Länder for making available their results of organochlorine pesticide analysis in human milk samples.

II.5.11. Exposure of children to contaminants: In vitro determination of oral bioavailability of toxic substances in soil

Agnes G. Oomen, Jacqueline G.M. van Engelen

Children ingest daily on average 50-200 mg of soil via hand-to-mouth behaviour.

Hence, ingestion of soil is considered a major route of exposure to many soil-borne contaminants. Oral bioavailability of ingested soil contaminants is defined as the contaminant fraction that reaches the systemic circulation. Oral bioavailability can be divided in four major processes. After soil ingestion, contaminants can be partially or totally released from soil into chyme, i.e. digestive juice, during digestion. The fraction that is mobilised from soil is defined as the bioaccessible fraction, and is considered to represent the contaminant fraction that is available for intestinal absorption. Bioaccessible contaminants can subsequently be absorbed, i.e. transported across the intestinal wall, and transferred into the blood (or lymph) stream. The contaminants may be biotransformed and excreted in the intestinal epithelium or liver. This is referred to as first-pass effect. After these steps, the contaminants reach the systemic circulation and thereby the rest of the body, and may exert toxicity.

Consequently, oral bioavailability of soil contaminants is the result of soil ingestion, bioaccessibility, absorption, and first-pass effect.

In present risk assessment of soil, oral bioavailability from soil is assumed to be equal to bioavailability of the contaminants from the matrix used in toxicity studies upon which human risk assessment is based. In toxicity studies typically food and liquid matrices are used. In literature it is suggested that oral bioavailability of contaminants from soil can be significantly lower. For that reason it was aimed to develop a tool for estimation and prediction of (a process of) oral bioavailability. This can be used to include the matrix of ingestion in risk assessment using a relative bioavailability factor, i.e. oral bioavailability or the contaminant in the matrix used in toxicity studies relative to the oral bioavailability or the contaminant in the soil matrix. The research of various institutes focuses on a tool that can simulate bioaccessibility as this process is assumed to be matrix dependent. For that reason, several in vitro digestion models have been developed.

The more complex models can simulate more aspects of human physiology whereas the simple models are easy to perform and allow simultaneous determination of large numbers of samples. At the present it is clear that many models exist with various experimental designs. The consequences of the different designs with regard to bioaccessibility values have recently been investigated (Oomen et al., submitted).

Bioaccessibility of soil contaminants is in many cases $< 50\%$, indicating that reduction of bioavailability can have implications for health risk assessment.

II.5.12. Estimating non-dietary ingestion of toxic substances in children

Jacqueline G.M. van Engelen, G. Wolterink and M.T.M. van Raaij

More than adults, children may be exposed to toxic substances, because children may spend more time in the same room or area, are in closer contact with a contaminated surface (e.g. by crawling), display more hand-to-mouth behaviour, and display less hygienic behaviour (e.g. mouthing of objects/surfaces, pica behaviour). In order to safeguard the use of toxic substances, risk assessments have to be performed. For this purpose, consumer exposure models such as CONSEXPO 3.0 (van Veen et al. 2001) have been developed to estimate exposure levels. CONSEXPO calculates (systemic) exposure levels through the inhalatory, dermal and oral routes. Furthermore, CONSEXPO allows calculation of exposure levels using different types of products (e.g. paints, insecticide spray cans), and different application scenarios (e.g. using a spray can for general surface treatment or spot application). When specific data for exposure to substances are lacking, which is often the case, default values for a specific exposure scenario are used in CONSEXPO.

Because hand-to-mouth contact is an important route for children exposure it is needed to gain insight in the processes involved in oral exposure through hand-to-mouth or object-to-mouth contact and to determine the most reliable and relevant method for assessment of exposure through hand-to-mouth contact. For this purpose, data from exposure experiments are collected, primarily by literature search. Based on these data default parametes for use in CONSEXPO can be determined.

Exposure to toxic substances can be estimated using both the macro-approach and the micro-approach. In both approaches experimentally determined transfer coefficients are used. However, the approaches differ in the level of refinement.

In the macro approach, exposure is the summation of all processes that contribute to transfer from surface to mouth. For instance, levels of the elements Al, Si, Ti in faeces can be used as a measure of daily soil intake. This approach has the advantage that estimation of the exposure is relatively simple. It should be noticed, however, that this method gives no insight in the contribution of each of the steps in the process of transfer, that the data are valid for a specific exposure scenario only, that extrapolation of data to other situations is difficult, and that exposure estimates may be based on rough assumptions.

The micro-approach uses detailed modeling of exposure as a series of separate transfers. For instance, the transfer of a toxic substance from a surface to the hand is determined by the concentration of the substance on the surface, the area of surface that comes in contact with the hand, the percentage dislodgeable substance, the frequency, duration and intensity of contact, and the surface area of the hand. Each of these transfer parameters may be subdivided into more refined transfer steps. For instance, the dislodgeable fraction of a substance depends on the structure of surface, chemical or electrostatic binding of the substance to surface, the time between application and hand contact, and whether the skin is wet, sticky or dry. The micro-approach has the advantage that it provides insight in the process of transfer of a substance from surface to mouth, and that extrapolations to other scenarios are possible. However, at present many parameters are unknown. Using worst-case estimates of every separate transfer parameter in the micro-approach may lead to very conservative exposure estimates.

In conclusion, data from the macro- as well as the micro-approach may be used as defaults in consumer exposure models such as CONSEXPO. However, the relevance of presently used defaults in exposure models is not very clear. Especially for the micro-approach, a large number of default parameters are unknown. Furthermore, refinement of

the defaults for the macro- as well as the micro-approach is necessary. Since data for most of the parameters of the micro-approach are lacking, at present exposure data from macro-approach are preferred.

References:

1. Van Veen M.P. CONSEXPO 3.0. Consumer exposure and uptake models. RIVM report 612810 011. RIVM, Bilthoven, The Netherlands, May 2001

II.5.13. Empirical evaluation in regard to differences in toxicokinetics between children and adults

Klaus Schneider

Human data for pesticides allowing for an in-depth analysis of possible differences in toxicokinetics between children and adults are lacking. But there are investigations carried out by various authors using data from pharmacokinetic studies with pharmaceuticals.

Hattis (2001) established a database and analyzed human pharmacokinetic data for 35 substances. He used the following age group definitions:

Premature neonates: ≤ 1 week, full term neonates: ≤ 1 week, newborns: 1 week - 2 months, early infants: 2-6 months, crawlers & toddlers: 6 months - 2 years, pre-adolescents: 2 -12 years, adolescents: 12 - 18 years.

Differences between age groups were analyzed with regard to following parameters: AUC (area under curve), C_{max} (maximum plasma concentration), (total) Clearance, T1/2 (elimination half life) and V_d (volume of distribution). For the first two parameters only a small amount of data was available. The following figure depicts the results of the evaluation of comparisons between adult values (set to 1) and the various age groups (mean and standard errors, derived from regression analysis of age group-specific data) for Clearance, T1/2 and V_d.

Neonates and newborns show higher values for elimination half times and lower clearance rates than adults, which is in accordance with the immaturity of the renal system of elimination. The opposite is true for older children from 6 months to 12 years showing a somewhat higher clearance. There is a tendency for a higher volume of distribution for the age groups up to 2 years compared to adults. This evaluation of Hattis (compare Chapter IV.1) hints on a higher internal body burden of children up to 6 months compared to adults.

The observation by Hattis (2001) of clearance rates for older children is in accordance with experiences from the paediatric chemotherapy. Several evaluations covering the last three decades and experience with about 50 anticancer drugs state higher maximum tolerated doses (MTD) for children compared to adults (Glaubiger et al., 1981; Marsoni et al., 1985; Carlson et al., 1996). Ratios of MTDs for children divided by MTDs for adults using MTDs expressed per m2 body surface are consistently > 1, indicating differences of > factor 2 if doses are transferred to a bodyweight base. Whereas toxicodynamic reasons (e.g. increased bone marrow reserve in children) may partly explain this observation, accordance with the evaluation of toxicokinetic data by Hattis (2001) point to a role for toxicokinetic reasons. The allometric principle of caloric demand scaling lead to the conclusion of a reduced body burden at the same magnitude (about factor 2 for elder children) as found in the evaluation of Hattis (2001) and the MTD comparisons mentioned above, if dose is expressed per kg bodyweight.

Renwick (1998) reached conclusions similar to Hattis (2001) by reviewing toxicokinetic data for a fast amount of pharmaceuticals. His analysis indicates that many drugs show reduced clearance and/or longer half lives in neonates, but greater elimination and higher clearance by infants and children compared to adults.

References:

1. Carlson, L., Ho, P., Smith, M., Reisch, J., Weitman, S., 1996 Pediatric phase I drug tolerance: a review and comparison of recent adult and pediatric phase I trials. Journal of Pediatric Hematology - Oncology, Vol. **18**, 1996, S. 250-256

2. Glaubiger, D. L., von Hoff, D. D., Holcenberg, J. S., Kamen, B., Pratt, C., Ungerleider, R. S., 1981. The relative tolerance of children and adults to anticancer drugs Frontiers of Radiation Therapy and Oncology, Vol. **16**, 1981, S. 42-49

3. Hattis, D., Russ, A., Ginsberg, G., Banati, P., Kozlak, M., Goble, R., 2001 Newborns, older children, and adults – comparisons of pharmacokinetics and pharmacokinetic variability Human Interindividual variability in parameters related to susceptibility for toxic effects. Http://www.clarku.edu/faculty/dhattis/, 2001

4. Marsoni, S., Ungerleider, R. S., Hurson, S. B., Simon, R. M., Hammershaimb, L. D., 1985
Tolerance to antineoplastic agents in children and adults. Cancer Treatment Reports, Vol. **69**, 1985, S. 1263-1269

5. Renwick, A. G., 1998 Toxicokinetics in infants and children in relation to the ADI and TDI. Food Additives and Contaminants, Vol. **15**, 1998, S. 17-35

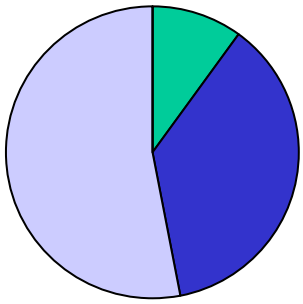
II.5.14. Protecting Children's Health: Science and Regulation

Gail Charnley

Q: Are children more sensitive : than adults to chemical toxicity?

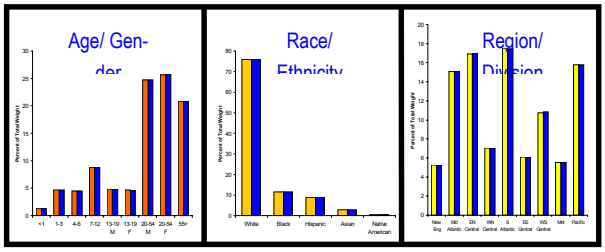
A: It depends on:

- the chemical
- the child's age
- the exposure situation



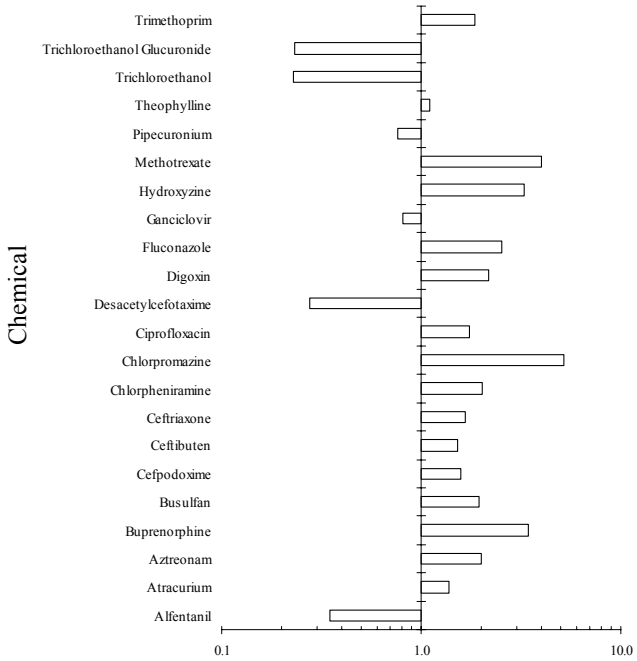
Effects of Age on Rodent Carcinogenesis
(Charnley and Putzrath, 2001)

CARES : software (Cumulative and Aggregate Risk Evaluation System) produces exposure estimates for multiple pesticides and multiple routes of exposure. The model matches pesticide exposure characteristics across data bases to generate individual year-long exposure profiles for 100,000 individuals, including children.



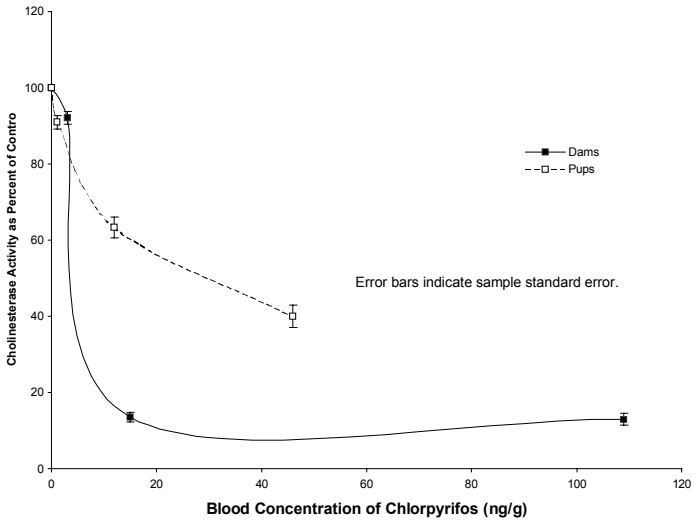
Children often have more rapid rates of drug metabolism and clearance than adults, but the differences are less than 5-fold. Chlorpyrifos : is an example of a substance that is less toxic to young animals than to adult animals at low doses, which reflect actual environmental exposures, although it is more toxic to young animals than adult animals at high doses.

Rates of Drug Metabolism: Comparison of Child and Adult (Renwick, 1998)



Ratio of Child to Adult Value (1 Indicates Unity)

Comparison of Forebrain Cholinesterase Activity : as a Function of Blood Chlorpyrifos Concentrations in Rat Dams and Pups (Mattsson et al., 2000)

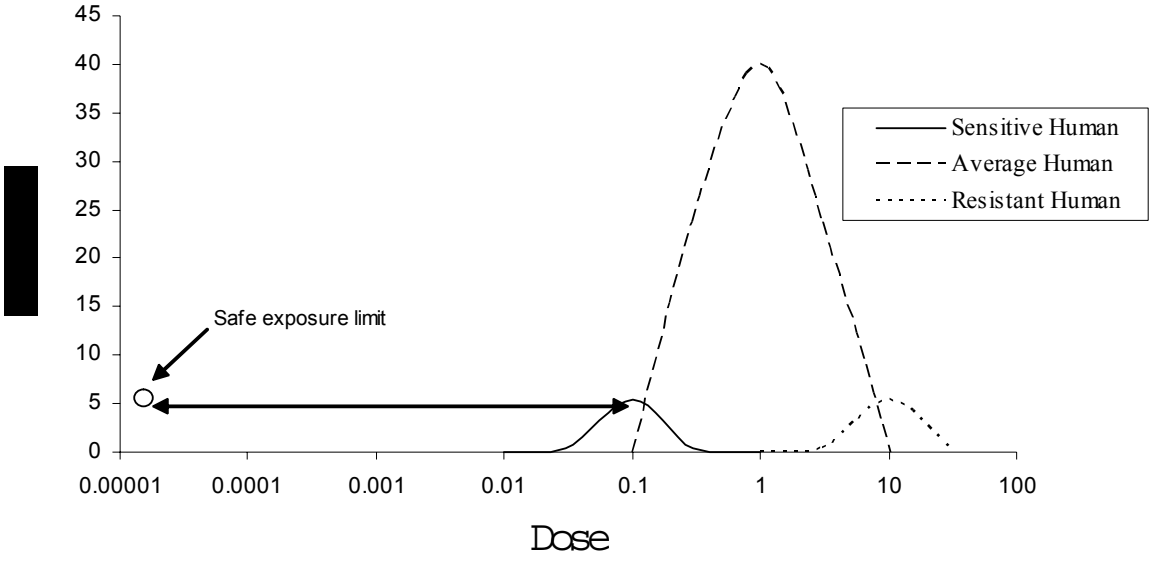


Q: Are children at greater ***risk*** of chemical toxicity than adults?

A: Only if their exposures exceed those required to produce toxicity.

Q: Are current regulatory approaches to limiting children's exposures to chemicals sufficient?

A: Most of the time (Dourson et al. 2002).



References

Charnley G, Putzrath RM. (2001) Children's health, susceptibility, and regulatory approaches to reducing risks from chemical carcinogens. *Environ. Health Perspect.* 109:187-192.

Dourson ML, Charnley G, Scheuplein R. (2002) Differential sensitivity of children and adults to chemical toxicity: II. Risk and regulation. *Reg. Toxicol. Pharmacol.*, in press.

Mattsson JL, Maurissen JP, Nolan RJ, Brzak KA. (2000) Lack of differential sensitivity to cholinesterase inhibition in fetuses and neonates compared to dams treated perinatally with chlorpyrifos. *Toxicol. Sci.* 53:438-446

Renwick AG. (1998) Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Addit.Contam.* 15:17-35

III. Conclusions drawn from the lecturers and posters

Open Presentation

Gerhard Heinemeyer

Introduction:

Children are no little adults. This general conclusion can be drawn very generally from the presentations and working group discussions of the workshop. The exposure to children, shown by the example of pesticides shows, that there are considerable differences between children and adults and that there are also a number of items that should be considered to describe this difference, as given in the table below:

1. The concentrations of the substances in the medium contacting the children, this includes.	
⇒ substances in air	ref. to chapter III.2.2
⇒ substances in dust and soil	ref. to chapter III.2.1, III.5.2, III.5.4, III.5.111
⇒ substances in food	ref. to chapter III.5.8, III.5.10
⇒ substances as article contaminations	ref. to chapter III.5.1, III.5.2
⇒ substances released from toys	ref. to chapter III.4.1
2. Behavíour of children, which is	
⇒ Moothing, sucking and biting	ref. to chapter III.1.3
⇒ Dietary and non-dietary ingestion	ref. to chapter III.5.10, III.5.12
⇒ Contact duration and frequency may differ to adult exposure	ref. to chapter III.1.3, III.4.1, III.4.2
3. Physiological developments	
⇒ Anthropometrics	ref. to chapter III.1.1
⇒ Toxicokinetics	ref. to chapter III.1.1, III.1.2, III.5.13
⇒ Toxicodynamics	ref. to chapter III.1.1
4. Variability of data in childhood	
⇒ Age dependent changes	ref. to chapter III.1.1, III.4.4
5. Biomonitoring	ref. to chapter III.3.2, III.5.3
6. Health effects	ref. to chapter III.3.3, III.3.4 III.5.9

The main question that arises from the discussion is, if children differ from adults, are they more sensitive? The answer is, they are not generally more sensitive, because sensitivity depends on age, developmental status and is ruled by the toxic characteristics of the substances.

In this context, the following questions have to be answered:

1. How to act substances on children?

   This question includes the discussion about toxic effects, in relation to organ development.

2. How do children process substances?

This question includes the discussion about absorption, distribution, and elimination (toxicokinetics), and other characteristic physiologic parameters that limit exposure and parameters the exposure is related to, which includes the so called anthropometric data (bodyweight, body surface, breating volume, alveolar surface).

3. How does behaviour of children limit exposure?

Quantification of exposure:

Exposure can be principally distinguished to (i) external exposure, describing the amount of a substance which is in contact with the person and (ii) internal exposure, describing all the processes of absorption, distribution, metabolism, and elimination. These factors govern the extent of exposure which can be either measured or modeled. Both methods have advantages and disadvantages, and require lots of prerequisites. Biomonitoring can also play an important role for exposure assessment, as well as measuring blood levels.

How do substances act on children?

This question includes all the processes where substances are acting on the organism due to its toxic properties, the toxicodynamics. In children, this must be directed to the effects of it's own and to include the developmental changes of organs during childhood as well.

Although the details are discussed under chapter II.1.1, a few items should be highlighted here.

An impression on the developmental aspects during the lifespan of childhood is given in Fig 1. It is shown that the development of the different systems does not happen in parallel, but in a very different manner. For instance, the CNS will mature during the first 4 to 6 years, with a rapid increase in the first two years, and a slow further increase between 10 and 18 years. In this age, however, the growth of the endocrine glands take place, in parallel with the hormonal secretion. Interestingly, there is an overgrowth of the lymphatic system during childhood as compared to adults.

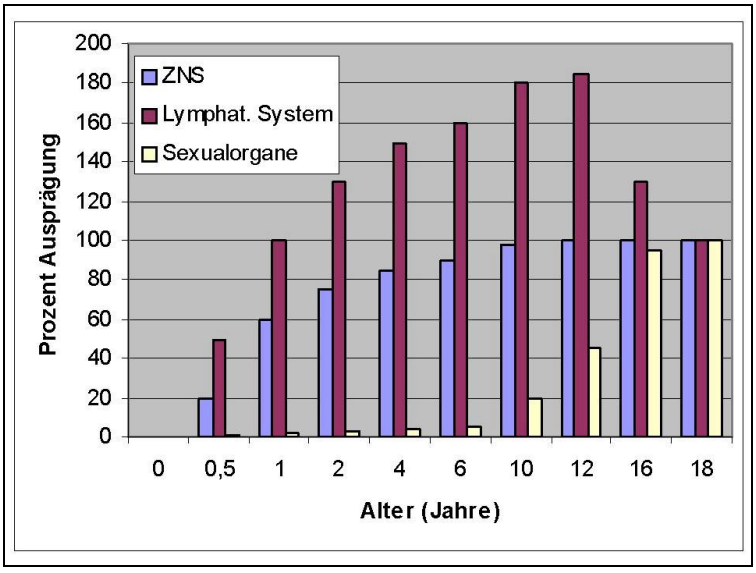


Figure 1: Development of some human organ systems throughout childhood

(adapted from "Fanconi, Wallgren, Lehrbuch der Kinderheilkunde, 1968)

From this illustration it is clear that effects of substances having influence on the organ systems must be different during different ages, in quality, quantity and due to duration and frequency of contact. It must be assumed that the reversibility of effects can also be due to the developmental status.

How do children process substances?

The main item that has to considered answering this question is how substances are absorbed, distributed, and eliminated which is characterised as the „kinetics“ of the substance. Dependent on the path of exposure, substances will be absorbed by the skin, via the lungs and in the gastrointestinal tract. Because absorption is mostly limited by the nature of the substance (e.g. water or lipid solubility) there may be differences in absorption due to the ageing of skin. Valid absorption studies do not exist that compare absorption in children and adults. Nevertheless, from a number of drugs we know that many substances can be absorbed very quickly and efficiently pass the dermal barrier and thus enter the systemic circulation.

Distribution of substances may also be different in children and adults which parallels the development of extracellular water compartments and the distribution in body fat.

The most important difference between children and adults, however, can be shown for the elimination of substances. In many cases, especially for drug metabolism, it was shown that children in the age between 1 and 5 years have the highest metabolic capacity of the whole lifespan exceeding that of adults 4 to 10 fold. This means that children will eliminate certain substances faster than adults and that toxic effects do not occur if the same doses are taken as referred to bodyweight. On the other hand, if toxic metabolites are formed, this may lead to increased toxicity in children.

Toxicologic evaluations are normally performed with reference to bodyweight. It is, however, well known that there is good correlation of most of the body functions e.g. basal metabolism with the body surface. This is also true for the metabolism of substances. For comparisons between children and adults it is therefore important to consider the age dependent changes in the bodyweight and the surface. For dermal exposures, the relative higher body surface thus results in relative higher absorbed amounts of substances in children.

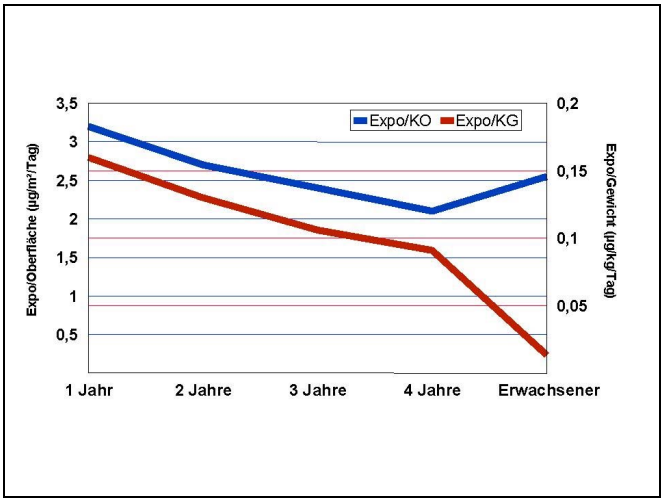


Figure 2: Age dependent exposure in one to four- year old children with permethrine from uptake of dust. Comparison to adults and reference to bodyweight and body surface (95th percentiles).

The permethrin dust concentrations were taken from Schomberg et al., (10), and multipied by dust uptake (Calabrese et al, 6, 2). Bodyweight (BW) was taken from the AUH report (1) and the body surface (BS) was calculated according the AUH-Data by the formula

$BS = 0.0239 * H^{0.,417} * W^{0.517}$ *(1).*

Furthermore, it has been stated (II.1.1) that the respiratory volume is much higher in children if referred to the lung surface which means that the inhalation exposure may be much higher in children than in adults.

Routes of exposures to children in households

There are several routes of exposures with pesticides in households important for children, the most important sources for children given below:

- Carpets household dust (Carpets have been suggested to be a sink for pesticides)
- Soil track in
- Pets (treated with pesticides)
- Clothing of pesticide users in a family
- contamination of food

Childrens behaviour

Children's behaviour may be one of the most important factors modulating exposure. Only a few studies have been performed. Close to children's behaviour, the problem of contamination of dust and soil must be mentioned. Substances that do not volatilise bind to carriers which are in the surroundings. For indoor situations, dust represents an important carrier. It occurs in two forms, as floating dust which can be inhaled or as house dust which is on the ground e.g. carpets or behind furniture. If substances are bound to dust, they can be uptaken together with the dust. Behaviour of children may lead to an increase of exposure by contact with dust, either by crawling, playing on the ground and by subsequent „hand-to-mouth-contact". In addition, hand-to-mouth behaviour leads to exposure from other sources particularly pets.

This type of behaviour should be taken into consideration for the assessment of exposure to children and can be taken to characterise to following scenarios due to age.

Variability of exposure

Variability of exposure is greater in children than in adults. This is due to the developmental changes in physiological parameters (bodyweight, body surface, breathing volume, toxicokinetics, -dynamics, as well as behaviour).

From this reason, it should be appropriate not to say children, but to differentiate several ages, an approach which has been proposed by working group one.

Another possibility to consider the variability of exposure in childhood is the use of the probabilistic approach. This means that the distribution of the exposure factors used for estimations should be characterised well and taken for calculations. It must be considered, however, that for taking this approach, the fundamentals of statistics and epidemiology must be kept in mind. Data must be characterised well and represent the population of interest. Considering this rules, probabilistic approaches offer a powerful tool for exposure estimations by modeling.

Other model approaches monitor exposures over long times and can thus differentiate between seasonal, but also daily activities. The models differentiate also between so called (i) macroactivities which describe roughly the time dependent stay of persons in their homes, otherwise called time budgets, and (ii) microactivities differentiating the above mentioned specific behaviour patterns e.g. the hand to mouth exposure. The long term models are developed and studied primarily in the US.

Health effects due to pesticide exposures

Most of the reported health effects related to exposure from pesticides are acute effects. The poison information centres have data mostly on short term single exposures, with specific symptomatology. Calls concerning exposures with pesticides account for about 3% of the calls in the centres of Lille (France) and Göttingen (Germany). As shown by the data from the Göttingen centre, 1/3 of that calls referred to exposures to children. In children, 87 % of calls are without symptoms, 12 % showed minor and 1% moderate symptoms. These data indicate that diseases due to pesticides exposure are already occuring, but real severe cases are seldom and related to acute overdosage.

Interestingly, no participant in the workshop was able to demonstrate a clear incidence for health effects from chronic exposures, although lots of measurements are available that show a substantial external exposure. Biomonitoring data do not correlate with dust concentrations measurements This may lead to the conclusion that dust may represent an important sink for some pesticides, but this source does probably not significantly contribute to overall exposure. Data from the BgVV showed evaluations of chronic exposures to pesticides. The data were taken from a spontaneous reporting system, with differentiation of the pesticide groups organophosphates and pyrethroids in an adult cohort with chronic low dose exposure. Interestingly, there was no difference between the two groups of exposures, and the symptoms were very similar to that reported in the literature occuring due to chemical sensitivity syndroms. Taken from these evaluations, there are no data available clearly showing an convincing evidence for the existence of health effects due to chronic low dose exposures.

Future of exposure assessments

The most important work that should be done in the future can be discussed according to the following three items:

1. Measuring or modeling exposure?

   For consumer exposures, only very few data on measured exposures are available. It is not clear whether models represent reality and adequately describe the circumstances of exposure. Due to high costs and operating expenses, consumer exposure must be modeled, however, the model approaches have to be validated. This means that for representative examples, modeled exposures should be verified by experimental measurements of exposure by comparing measured and modeled results. This has been performed for some scenarios of exposures with volatile substances but not with non-volatile substances.

   An easier way to improve the knowledge are measurements of single exposure factors e.g. migration rates, room ventilation, concentrations of substances in dust. If these measurements are representative for a scenario they should be preferred for model evaluations.

2. Data compilation

   One of the most important problems for exposure estimations is that data for modeling are incomplete and therefore uncertain and not representative, neither for a given scenario nor for a population or region.

   For some data, sufficient data bases exist e.g. some anthropometrics (bodyweight, body surface). Data are sufficiently available for product use and composition, behaviour of people, micro- or macroactivities, or room sizes including ventilation. For US, EPA has published the EPA-Exposure factors handbook, for Europe some documents exist such as the AUH-report (1), as well as reports from the dutch RIVM (3, 4), the danish EPA (9) and from industry (7).

3. Uncertainties and variabilities

It is assumed that some problems of exposure assessment can be solved when taking uncertainty and variability of data into account. This applies in particular for the discussion of worst case evaluations. The worst case approach does only work if the worst case assumption, that is the deterministic value which is put into the model, is clearly described as an extreme of the distribution. This clearly means that without characterisation of a distribution of the exposure factor a worst case assumption is uncertain and unvalid. From the scientific view, the first step in the characterisation of an exposure factor is the description of the distribution and of it's statistical fundamentals. Probabilistic approaches should therefore be given priority for data characterisation.

References:

1. American Industrial Health Council (1994) Exposure Factors Sourcebook. Suite 760, 2001 Pennsylvania Ave., NW, Washington DC 20006-1807
2. Ausschuss für Umwelthygiene (AUH) (1994) Standards zur Expositionsabschätzung. Arbeitsgemeinschaft der leitenden Medizinalbeamtinnen und -beamten der Länder, Behörde für Arbeit, Gesundheit und Soziales, Hamburg
3. Bremmer H.J. and Van Veen M.P. (2000a) Factsheet algemeen, randvoorwaarden en betrouwbaarheid, ventilatie, kamergrootte, lichaamsoppervlak [General Factsheet, conditions and reliability, ventilaiton, room size, body surface]. RIVM report 612810 009, RIVM, Bilthoven, The Netherlands.
4. Bremmer HJ, van Veen MP (2000b) Factsheet Verf. Ten behoeve van de schatting van de risico's voor de consument. RIVM rapport 612 810 010
5. Calabrese EJ, Pastides H, Barnes R, Edwards C, Kostecki PT, Stanek III EJ, Veneman P, Gilbert CE (1989) "How much soil do young children ingest: an epidemiological study". Reg Toxicol Pharmacol 10, 123-137
6. Calabrese EJ, Barnes R, Stanek III EJ, Pastides H, Gilbert CE, Veneman P, Wang X, Lasztity A, Kostecki PT (1989) "How much soil do young children ingest: an epidemiological study". in: E.J. Calabrese and P.T. Kostecki (eds) Petroleum Contaminated soils: Volume 2, Chapter 30, 363-397
7. ECETOC (2001) Exposure factors sourcebook for european populations (with focus on UK data). Technical report No. 79.
8. Environmental Protection Agency (1997) Exposure Factors Handbook. Update to Exposure Factors Handbook EPA/600/8-89/043 – May 1989. Office of Research and Development, National Center for Environmental Assessment. Vol. I-III. EPA/600/P-95/002Fa, August 1997, Washington, DC
9. Larsen PB, Nielsen E, Thorup I, Schnipper A, Hass U, Meyer O, Ladefoged O, Larsen JC, Østergaard G (2001) Children and the unborn child. Environmental Project 589 2001. Danish Environmental Protection Agency.
10. Schomberg K, Winkens A (2000) Zur Belastung rheinländischer Haushalte mit Permethrin. Umweltmed Forsch Prax 5, 331-335

Open Presentation

IV. Results from workshop working groups

IV.1. Working group 1: Children as a vulnerable group

Chairperson: Wayne R. Snodgrass

Rapporteur: Frederic Bois

Co-rapporteur: Gail Charnley

Further working group members: Nida Besbelli, Axel Hahn, Monique Matthieu-Nolf, Martin Wilks, Herbert Desel, Joanne Hughes, Rainer Konietzka, Klaus Schneider

Open Presentation

Note: it was decided to not discuss the prenatal period and to not differentiate biocides and pesticides.

There are definite reasons for differences in sensitivity to toxicants between adults and children. Those differences can lead to increased or decreased sensitivity. This section documents differences that appear most relevant to pesticides, and stresses the lack of relevant data. The interpretation of the few data available can be controversial, as we experienced it within our working group. We are however unanimous at emphasising the need for additional specific data on children or young animals.

A first task of the group was to define age groups (source of this classification: BgVV). Table 1 is given for reference. It was also decided to not discuss the prenatal period and to not differentiate biocides from pesticides.

Table 1: Definition of human age groups (source: BgVV)

Premature infant	≤ 36 weeks (of gestation)
Newborn	1 - >28 days (after birth)
Infant	29 days - 1 year
Small child	1 - < 6 years
School child	6 - < 14 years
Adolescent	14 - < 18 years
Adult	18 - < 65 years
Senior	> 65 years

IV.1.1. Why may children be more or less susceptible to chemical toxicity than adults?

Human data for pesticides allowing for an in-depth analysis of possible differences in toxicokinetics between children and adults are lacking. But there are investigations carried out by various authors using data from pharmacokinetic studies with pharmaceuticals.

Hattis et al. (2001) established a database and analysed human pharmacokinetic data for 35 substances. He used the following age group definitions:

Premature neonates: ≤ 1 week, full term neonates: ≤ 1 week, newborns: 1 week - 2 months, early infants: 2-6 months, crawlers & toddlers: 6 months - 2 years, pre-adolescents: 2 -12 years, adolescents: 12 - 18 years.

Differences between age groups were analysed with regard to following parameters: AUC (area under curve), C_{max} (maximum plasma concentration), (total) Clearance, T1/2 (elimination half-life) and V_d (volume of distribution). For the first two parameters only a small amount of data was available. Figure 1 depicts the results of the evaluation of comparisons between adult values (set to 1) and the various age-groups (mean and standard errors, derived from regression analysis of age group-specific data) for clearance, T1/2 and V_d.

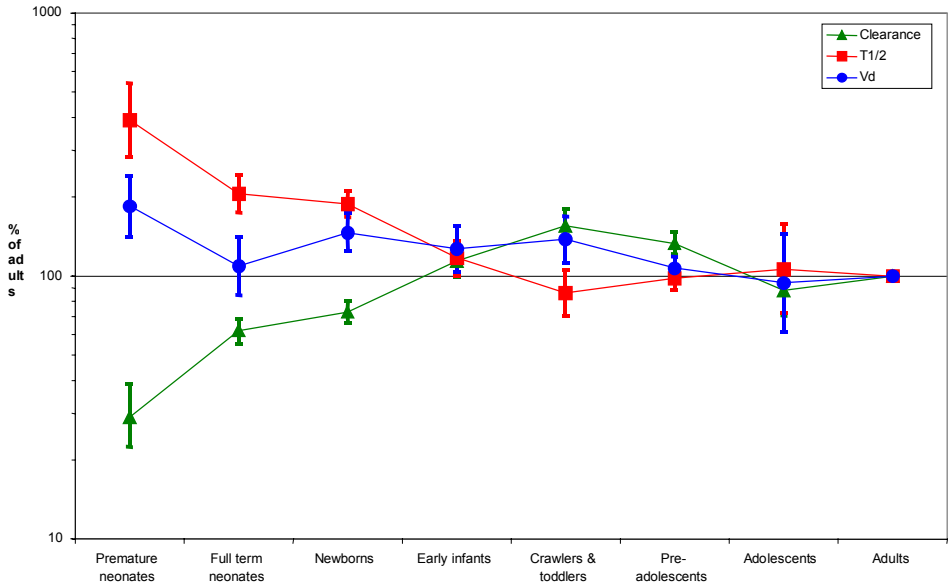


Figure 1: Mean values (and standard errors) for Clearance, T1/2, and V_d for different age groups compared to adults (data from Hattis et al., 2001)

Neonates and newborns show higher values for elimination half times and lower clearance rates than adults, which is in accordance with the immaturity of the renal system of elimination. The opposite is true for older children from 6 months to 12 years showing a somewhat higher clearance. There is a tendency for a higher volume of distribution for the age groups up to 2 years compared to adults. This evaluation of Hattis and coworkers suggests a higher internal body burden of children up to 6 months compared to adults. More recent work by the same authors confirm, for the drugs they studied, these findings (Ginsberg et al. 2002).

The observation by Hattis et al. (2001) of clearance rates for older children is in accordance with experiences from the paediatric chemotherapy. Several evaluations covering the last three decades and experience with about 50 anticancer drugs state higher maximum tolerated doses (MTD) for children compared to adults (Glaubiger et al., 1981; Marsoni et al., 1985; Carlson et al., 1996). Ratios of MTDs for children divided by MTDs for adults using MTDs expressed per m^2 body surface are consistently higher than 1, indicating differences of more than factor 2 if doses are transformed to a bodyweight base. Whereas toxicodynamic factors (*e.g.*, increased bone marrow reserve in children) may partly explain the observed age-related differences in sensitivity, the evaluation of toxicokinetic data by Hattis et al. (2001) points to a role for toxicokinetic factors. The allometric principle of caloric-demand scaling suggests for many substances a similar reduction in body burden (about a factor of two for children older than 6 months), as was found by Hattis et al. (2001) and in the MTD comparisons mentioned above, if dose is expressed per kg bodyweight.

Renwick (1998) reached conclusions similar to Hattis et al. (2001) by reviewing toxicokinetic data for many pharmaceuticals. His analysis indicates that many drugs show reduced clearance and/or longer half lives in neonates, but greater elimination and higher clearance by infants and children compared to adults.

IV.1.2. What is known about age related differences in pesticide toxicity?

Young children may be more highly exposed than adults to pesticides found in the home environment, such as organophosphates (OPs), carbamates, organochlorines, and pyrethroids, because of their natural tendency to explore their environment orally. They are also in close proximity to potentially contaminated floors, surfaces, and air. Exposure might be further increased by children's higher intakes of food, water, and air per unit bodyweight when compared to adults.

As described in the NRC report "*Pesticides in the diets of infants and children*"(National Research Council, 1993), there are important biological reasons for differences in vulnerability of children, rendering children more susceptible to pesticide toxicity in some occasions:

- Children's metabolic pathways, especially in the first few months after birth, are immature compared to those of adults. In some instances this means that they are unable to metabolise compounds to their active forms, but more commonly means that they are less able to detoxify chemicals. On the other hand, for infants and children, many metabolic processes are actually increased compared to adults.
- Children are growing and developing and their developmental processes can be disrupted. For different organs there may be time periods during development that increase children's vulnerability. The length of the period and the children´s age at its start varies, depending on the organs. For example, neurotoxicity may be more likely during glial cell proliferation at age 1, while reprotoxicity may be more likely during puberty. If brain cells are destroyed, reproductive development diverted, or immune system development altered, the resulting dysfunction can be irreversible.

This section is concerned with the risk of health effects from exposure to pesticides that children face due to their developmental immaturity (Eskenazi *et al.*, 1999). Where available, examples of toxicities to which children are more or less susceptible than adults are given (*i.e.*, situations where, for a given plasma concentration of a pesticide, greater or lower toxicity is observed in children than in adults). Human and laboratory animal data on health effects following short-term high dose pesticide exposures and longer-term lower dose pesticide exposures are considered.

IV.1.2.1. Literature search

Datastar Medline and Embase were searched for human data with a year limit of 1991+. The search terms were tailored to the indexing used in each database as summarised in the table below. Only postnatal exposures were considered.

Datastar Medline: Pesticides# AND Child.de. Infant# School child$3.ti,ab. AND Vulnerab$5.ti,ab. Susceptib$5.ti,ab.

Embase: Pesticides# AND Child.de. # AND Vulnerab$5.ti,ab. Susceptib$5.ti,ab.

IV.1.2.2. Health effects following single, high-dose exposures to pesticides

Humans

Information with regard to pesticide poisoning for all ages is available from regional poison control centres. These data are generally restricted to acute clinical effects, and therefore do not include information on the potential chronic health effects that might be experienced by individuals once the initial acute symptoms have subsided. The data indicate that death following ingestion of high doses of pesticides is rare; in fact a large proportion of pesticide incidents involving children reported to poison control centres do not even result in minor effects. This is because the parents may only suspect that their child has ingested some pesticide, or the dose is so small that it does not cause adverse health effects. In many cases the dose received is never determined (Hayes & Laws, 1991).

Poison control centre data collected by the US Centers for Disease Control show that there is a higer potential for harmful exposures in young children than in older age groups, but they do not necessarily demonstrate an increase in the sensitivity of young children (US EPA, 1999). There is a possibility that young children may be exposed to higher doses on a bodyweight basis compared to adults (from spills, ingestion, inhalation) because they are ignorant of the hazard, and not because of differences in sensitivity based on age to the effects of these pesticides. Data from poisoning incidents are also likely to occur at doses much higher than those that would be expected from environmental exposures. For those reasons, it is difficult to draw conclusions from human incident data on the sensitivity of children compared to adults (US EPA, 2002).

There are numbers of examples of pesticides for which children appear to be more susceptible to poisoning than adults (NRC, 1993). On the other hand, OP-induced delayed onset peripheral neuropathy, reported in adults, has not been reported in children (Eskenazi *et al.*, 1999).

Laboratory animals

Experiments using laboratory animals demonstrate that young animals are more sensitive than adults to the acute toxic effects of some pesticides. The published literature provides lots of information that pertains to the relative sensitivity of young animals to OP and pyrethroid pesticides. The scope of these studies is generally limited to estimates of acute lethal doses. From LD_{50} values it can be concluded that neonatal rats are around nine times more sensitive than adults to certain OPs, and 20 times more sensitive than adults to certain pyrethroids (Sheets, 2000). For both of these groups of pesticides the higher susceptibility appears to be due to immature development of enzymes involved in detoxification.

Other acute toxicity studies in rats using lower acute doses have also shown age-related differences in sensitivity. For example, at one-half the LD_{10}, young animals are more sensitive to cholinesterase inhibition by chlorpyrifos, with newborn animals about threefold more sensitive than juveniles and nine times more sensitive than adults (Pope, 2001). Rat pups are also more sensitive than adults to cholinesterase inhibition by acute doses of diazinon, which has been correlated with their lower activities of detoxifying carboxylesterases and A-esterases (Padilla, et al. 2002). In contrast, neonatal rats are not more sensitive than adults to cholinesterase inhibition by acute doses of dimethoate or methamidophos (Meyers, 2001, Moser, 1999).

Whitney *et al*. (1995) found that administration of chlorpyrifos to neonatal rats at 1 day of age (approximately 7 months of gestation in humans) produced significant inhibition of DNA and protein synthesis throughout the brain. The authors interpreted this as a targeting of the developing brain during the critical period in which cell division occurs. Most

studies on the developmental effects of OP pesticides use chlorpyrifos; therefore, it is not clear whether developmental neurotoxicity is a class effect. The US Environmental Protection Agency has concluded on the basis of currently available data that, as a class, OPs are not developmental neurotoxicants at doses below those that produce cholinesterase inhibition (US EPA, 2002).

IV.1.2.3. Health effects following repeated, lower exposures to pesticides

Humans

The potential for pesticides to cause low-level toxicity is a controversial area of toxicology and is an area that is extremely difficult to study. It is hampered by a number of factors such as difficulty in measuring actual exposure levels, confounding due to simultaneous exposure to a range of different pesticides and other chemicals, length of time between exposure and appearance of symptoms, and the diverse nature of the symptoms observed (POST, 1998). To compound the difficulties in studying this area, there is a paucity of research in children, mainly because of the ethical issues involved.

There are no data in children to support or refute the hypothesised health effects of chronic, low-level (doses that do not produce clinical signs of toxicity) pesticide exposure. Most human studies are epidemiological studies of individuals exposed occupationally. Where children have been studied, there are problems with exposure characterisation and confounding factors. However, on the basis of various sources of information not pertaining to pesticides, it seems possible that children are, in some circumstances and for some chemicals, more vulnerable than adults (*e.g.,* as mentioned above, because of windows of vulnerability in developing organ systems *etc.*).

Evidence that neonates are more sensitive than adults to OP and pyrethroid pesticides is largely based on studies that compare toxicity at acute lethal doses. This greater susceptibility is likely to be due to limited metabolic capacity rather than an inherent difference in the sensitivity of the target tissues.

Laboratory animals

Most information on chronic effects of any chemical tend to come from studies on laboratory animals. These generally use comparatively high doses and do not start administration of the test compound until the animals are several weeks old. Studies using newborn rats are of questionable relevance to human newborns because the developmental periods and milestones are not correlated. As a result, extrapolation of the results of laboratory animal studies of pesticides to human infants and children is difficult.

In contrast to the studies of pesticides' acute toxicity, higher sensitivity of adult animals to the effects of repeat doses of chlorpyrifos (by a factor 2 to 5 compared to young animals) have been reported,,at least for some endpoints (acetylcholinesterase inhibition but not bodyweight changes). Zheng et al. (2000) reported that chlorpyrifos produced a minimal difference in cholinesterase inhibition in newborn rats compared to adults following repeated dosing, with a 1.5-fold increase in brain cholinesterase inhibition seen in newborns based on ED_{50} levels. Smaller increases were seen in newborn rats compared to adults administered chlorpyrifos by subcutaneous injection for 7 days, and no age-related differences were seen after 14 days' treatment (Liu et al., 1999). In contrast, newborn rats were more sensitive to methyl parathion than adults using the same protocol (Liu et al., 1999). Rats exposed to dimethoate in utero, through lactation, and then by gavage until postnatal day 21 showed no differences in brain and plasma cholinesterase inhibition when young and adult animals were compared (Meyers, 2001), although rats exposed similarly to methyl parathion showed that young rats were more sensitive than adults (Beyrouty, 2002).

In a review of neonatal sensitivity to OPs and pyrethroids, Sheets (2000) concluded that, for OPs, adults were affected to a greater extent at a given dietary level than was the neonate or weanling. For pyrethroids, neonates were more sensitive to an acute lethal dose, but not to the much lower levels that would be relevant to human dietary risk assessment.

In the case of OPs, the smaller age-related differences in pesticide toxicity observed following lower, repeated doses as compared to higher, acute doses is likely to be due to the ability of developing animals to recover more quickly from cholinesterase inhibition because they can synthesize cholinesterases faster than adults (Ashry et al., 2002, Abu-Qare et al,. 2001). This conclusion is supported by the observations of Liu et al. (1999), who found that repeated chlorpyrifos exposures were associated with relatively similar degrees of cholinesterase inhibition among age groups during dosing but found more extensive inhibition in adults after termination of exposures.

Discrepancies among studies might be explained by different exposure schedules and doses, with higher acute doses producing more toxicity in younger animals than lower, repeated doses. Studies in which young animals were found to be more sensitive to the cholinesterase-inhibiting effects of OPs were conducted using doses that are as much as 100,000 times greater than environmental exposure levels (US EPA, 2002). It is plausible that high doses of OPs overwhelm the developing rat's immature detoxification mechanisms. Studies conducted at more environmentally relevant doses, which would be less likely to overwhelm the young rat's ability to detoxify OPs, show that young animals are of similar sensitivity to adults (Mattsson et al., 2000).

IV.1.2.4. Other factors for consideration

Most commercial products that are used as pesticides are marketed as formulations and therefore contain vehicles and other chemicals added to give the pesticide optimum properties for the desired use. These added compounds cannot be assumed to be inert. Indeed, the toxicological properties of the added ingredients may in some instances be more important than those of the pesticide active ingredient. The toxicity of the active ingredient may be modified by differences in formulation. Solvents are particularly important; they may increase or decrease the potential toxicity of a pesticide by altering its absorption. Hence the toxicity of each compound should be tested (or at least a risk assessment conducted) for every formulation in which it will be used (Hayes & Laws, 1991).

IV.1.3. How should age-related differences in susceptibility be accounted for in pesticide safety assessment?

IV.1.3.1. Dose considerations - Toxicokinetics

Children can activate or detoxify substances at different rates than adults. This affects effective dose. More precisely, newborns have immature metabolic capacities and their renal excretion capacity is no fully developed. The consequence of these differences may be a higher pesticide body-burden. The situation seems to be opposite for older children. On a bodyweight basis body-burden seems to be somewhat lower compared to adults due to a higher rate of renal excretion. But these generalizations give only central tendency estimates. The actual behaviour of single substances may deviate from this.

Development of the various metabolic systems is relatively well characterised and on that basis one can infer whether children's effective doses of a particular substance will be larger or smaller than that for adults' for the same exposure. In the absence of toxicokinetic data the hypothesis that children are more susceptible than adults should be given careful consideration.

IV.1.3.2. End-point considerations

Toxicity end-points can be childhood-specific, or can occur later in adult life as a consequence of childhood exposure. Relevant end-points can be neurologic, immunologic, cancer, or other target-organ toxicity.

Due to phases of rapid organ development children may be more susceptible than adults to a substance's toxic effects. These differences in susceptibility may be quantitative in nature (effects may occur at lower doses than in adults) or qualitative (effects will not occur at all in adults). Typical example from the drug area include the effects of tetracycline on children's teeth and bones, and of fluoroquinolones on bones.

There are basic toxicity data available for most pesticides and many have an extensive database. Such data provide indications on the potential mode of action and target organs of toxicity and should be used to infer likely developmental toxicity. They can also be used to guide a tiered approach to further data generation. Available data should be screened for organ toxicities especially critical for children. New tests, like the developmental neurotoxicity test (DNT), may be helpful in this respect, although whether DNT tests provide more information for pesticide safety assessment than can be obtained from carefully conducted standard developmental toxicity tests is controversial.

IV.1.3.3. Acute vs. chronic effects

Pesticide exposures can produce both acute and chronic effects and it may not be possible to generalise from one type to the other. This conclusion is corroborated by the chlorpyrifos example discussed earlier. If both types of exposure (acute vs. repeated) are important experimentally or environmentally, both should be evaluated for risk assessment.

IV.1.3.4. Risk management context

When data on age-related susceptibility differences are available, their use should be consistent with risk management goals.

- Are separate ADIs sought? Some members of the panel were of the opinion that separate ADIs for children are not helpful, because ADIs should generally be applicable for the whole population and children are a part of it. (In most cases data are lacking for a meaningful differentiation anyway).
- Are larger margins of exposure needed for children? The risk management goal sought and the biological data in support of the assessment strategy should be clearly stated when choosing the margin of safety or the size of uncertainty or safety factors.
- Should dose-response assessments be adapted to account for age-related differences? Where meaningful age-related dose-response data are available, they should be used.
- Should such information on age-related differences be included in stochastic analyses? In the opinion of some panel members, available biological data (on toxicokinetics, on observed differences between age groups seen with drugs) should be used to describe distribution functions for children. These distribution functions may be an important input for probabilistic risk assessment methods (Vermeire et al., 1999). These methods can provide information useful to define appropriate levels of protection.

IV.1.4. Data Available / Data Needed

Standard regulatory toxicity protocols start with "teenage" animals instead of infants, do not characterise age-related differences in susceptibility, and use high doses instead of environmentally relevant doses (although susceptibility differences are often dose-dependent).

The following information sources are available and should be fully used when assessing a substance's potential risks to children:

- Literature searches
- Mining of human data for information on:
- Therapeutic use of pesticides,
- Chemical class effects, by analogy to pharmaceuticals,
- Better use of poison-centre data.

The following lines of action could be explored:

- Extend existing study protocols to evaluate specifically very young animals,
- Obtain more information about low-dose chronic (sub-clinical) effects in humans,
- Set-up dedicated surveillance systems for children poisoning accidents,
- Evaluate in greater details he differences due to age on bone marrow toxicity, cancer, endocrine effects, and allergenicity from pesticide exposures,
- Improve the exposure data used in epidemiological studies (and their age specificity).

IV.1.5. References

Abu-Qare AW, Abou-Donia MB, 2001, Inhibition and recovery of maternal and fetal cholinesterase enzyme activity following a single cutaneous dose of methyl parathion and diazinon, alone and in combination, in pregnant rats. J Appl Toxicol **21**:307-316.

Ashry KM, Abu-Qare AW, Saleem FR, Hussein YA, Hamza SM, Kishk AM, Abou-Donia MB, 2002, Inhibition and recovery of maternal and fetal cholinesterase enzymes following a single oral dose of chlorpyrifos in rats. Arch Toxicol **76**:30-39.

Beyrouty P, 2002, A study on the effects of orally administered methyl parathion on cholinesterase levels in adult, juvenile, and neonatal rats. ClinTrials BioResearch Ltd., Senneville, Quebec. Lab Project Number: 97558, February 26, 2002, MRID 45656501.

Carlson L, Ho P, Smith M, Reisch J, Weitman S, 1996, Pediatric phase I drug tolerance: a review and comparison of recent adult and pediatric phase I trials, Journal of Pediatric Hematology - Oncology, **18**:250-256.

Eskenazi B, Bradman A & Castorina R, 1999, Exposures of children to organophophate pesticides and their potential adverse health effects, Environ Health Perspect, **107**(suppl 3):409-419.

Ginsberg G, Hattis D, Sonawane B, Russ A, Banati P, Kozlak M, Smolenski S, Goble R, 2002, Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature, Toxicol Sci **66**:185-200.

Glaubiger D.L., von Hoff D.D., Holcenberg J.S., Kamen B., Pratt, C., Ungerleider, R.S., 1981, The relative tolerance of children and adults to anticancer drugs, Frontiers of Radiation Therapy and Oncology, **16**:42-49.

Hattis D., Russ A., Ginsberg G., Banati P., Kozlak M., Goble R., 2001, Newborns, older children, and adults – comparisons of pharmacokinetics and pharmacokinetic variabi-

lity Human Interindividual variability in parameters related to susceptibility for toxic effects. http://www.clarku.edu/faculty/dhattis/.

Hayes WJ.Jr. & Laws ER.Jr., eds, 1991, Handbook of Pesticide Toxicology, Volume 1, General Principles, London, UK, Academic Press.

Liu J, Olivier K, Pope CN, 1999, Comparative neurochemical effects of repeated methyl parathion or chlorpyrifos exposures in neonatal and adult rats, Toxicol Appl Pharmacol, **158**(2):186-96.

Marsoni S., Ungerleider R.S., Hurson S.B., Simon R.M., Hammershaimb L.D., 1985, Tolerance to antineoplastic agents in children and adults, Cancer Treatment Reports, **69**:1263-1269.

Mattsson JL, Maurissen JP, Nolan RJ, Brzak KA, 2000, Lack of differential sensitivity to cholinesterase inhibition in fetuses and neonates compared to dams treated perinatally with chlorpyrifos, Toxicol Sci **53**:438-446.

Meyers D, 2001, Dimethoate effects on cholinesterase in the CD rat (adult and juvenile) by oral gavage administration, Huntingdon Life Sciences, Ltd., Suffolk, England, Lab Project Number: CHV/070: 012226, MRID 45529702.

Moser VC, 1999, Comparison of aldicarb and methamidophos neurotoxicity at different ages in the rat: behavioral and biochemical parameters, Toxicol Appl Pharmacol. **157**(2):94-106.

National Research Council, 1993, Pesticides in the Diets of Infants and Children, Washington DC, USA, National Academy Press.

Padilla S, Sung H-J, Jackson L, Moser V, 2002, Development of an *in vitro* assay which may identify which organophosphorus pesticides are more toxic to the young, Presented at the Society of Toxicology meeting, March 2002.

Pope C, 2001, The influence of age on pesticide toxicity, In *Handbook of Pesticide Toxicology* (ed. R. I. Krieger) Volume 1, Principles Chapter 41, Academic Press, pages 873-885.

POST, 1998, Organophosphates (POSTnote 122), London, UK, Parliamentary Office of Science and Technology.

Renwick A.G., 1998, Toxicokinetics in infants and children in relation to the ADI and TDI-Food Additives and Contaminants, **15**:17-35.

Sheets L.P, 2000, A consideration of age-dependent differences in susceptibility to organophosphorus and pyrethroid insecticides, Neurotoxicology, **21**:57-64.

Smialowicz R.J., Riddle M.M., Rogers R.R., Luebke R.W., Copeland C.B., 1990, Immunotoxicity of tributyltin oxide in rats exposed as adults or pre-weanlings, Toxicology, **57**:97-111.

Smialowicz R.J., Riddle M.M., Rogers R.R., Rowe,D.G., Luebke R.W., Fogelson L.D., Copeland C.B., 1988, Immunologic effects of perinatal exposure of rats to dioctyltin dichloride, Journal of Toxicology and Environmental Health, **25**:403-422.

US Environmental Protection Agency (EPA), 1999, Memorandum from Jerome Blondell, Office of Pesticide Programs, Health Effects Division to Dennis Utterback, of the Office of Pesticide Programs, Special Review and Reregistration Division, “Review of Poison Control Center Data for Residential Exposures to Organophosphate Pesticides, 1993-1996.” February 11,1999. Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances, Washington, DC.

US Environmental Protection Agency (EPA), 2002, Revised OP Cumulative Risk Assessment – 6/11/02. Office of Pesticide Programs. Office of Prevention, Pesticides, and Toxic Substances, Washington, DC.

Vermeire T, Stevenson H, Peiters MN, Rennen M, Slob W, Hakkert BC, 1999, Assessment factors for human health risk assessment: a discussion paper, Critical Reviews in Toxicology, **29**:439-490.

Whitney KD, Seidler FJ, Slotkin TA, 1995, Developmental neurotoxicity of chlorpyrifos: cellular mechanisms, Toxicol Appl Pharmacol, **134**:53-62.

Zheng Q., Olivier K., Won Y.K., Pope C.N., 2000, Comparative cholinergic neurotoxicity of oral chlorpyrifos exposures in preweanling and adult rats, Toxicological Sciences, **55**:124-132

Open Presentation

IV.2. Working group 2: Modeling exposure of children to pesticides

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Open Presentation

IV.2.1. Scenarios and models of exposure estimation, needs for data, uncertainty and variability.

A lot of information about modeling procedures for pesticide exposure in general and for children in particular is scattered among different (international) institutions (e.g. US EPA, European Union, biocide regulation etc.). There is a strong need to get an overview on which institutions, governments etc. have information about pesticide exposure modeling and bring them together and share there knowledge. The BgVV-workshop is a good start, a follow-up is urgently required.

IV.2.2. Exposure scenarios and models

The working-group agreed on using the risk assessment paradigm of the National Research Council (1983). The paradigm includes the components: hazard identification, exposure assessment, dose-response assessment and risk characterization. The discussion in the working-group focused on the identification of hazardous exposure scenarios and exposure assessment/modeling.

Children can be exposed to pesticides, especially in the residential environment. There are a number of children's characteristics, which influence exposure.

- physiological characteristics (see WG 1)

  larger surface area relative to bodyweight;

  higher basal metabolic (larger surface area and growth);

  permeability of the skin, highest at birth, similar to adults after 1 year;

  development of subcutaneous layer of fat (2-3 months until early toddler period);

  lung alveoli continue to develop until adolescence;

  absorption and permeability in the gut are regulated by the body to provide nutritional needs that vary with age (e.g. Ca absorption)

- behavioural development (see WG 4)

  mouthing behaviour;

  soil ingestion;

  contact with floor/carpet

- physical activities

  locations where a child spends time determine the exposure media that may be contacted and affect the activity level that determines contact rate with those media; additional variability among children of similar developmental stages is asso-

ciated with seasonal and geographic differences in activity patterns and the use of indoor and outdoor space

- diet and eating habits

  newborns breast milk or infant formula;

  infants and young children: more fruit and milk, phases of preferred food;

  eating with hands, eat foods fallen on the floor.

All these characteristics should be taken into account. For modeling exposure to pesticides, many exposure scenarios and sub-scenarios can be set up. The question arises, which scenario will be the most relevant one? This depends on the product characteristics (contamination, concentration and formulation), product use (application type and form, frequencies, duration), exposure pathways (breast-feeding, inhalation, food intake, dermal contact etc.), and exposure routes (oral, dermal, inhalation).

In every assessment all three possible exposure routes (oral, dermal and inhalatory) should be examined. Not in every case all three routes are relevant, e.g. in the case of exposure to pesticides via food, the oral route will be the main route of exposure. In case of exposure to a flea-spray that has been used to treat a carpet, children that crawl on that carpet can be exposed dermally, via the oral route (hand-to-mouth contact), and inhalatory (evaporation of the active ingredient). In contrast to the oral and inhalation route, the dermal exposure assessment methodology is not yet well developed. Apart from the above rather straightforward sources of exposure, there might also be more ‘hidden’ sources, e.g. house dust, which can form a sink for numerous chemicals.

Models for estimation of the exposure to pesticides should be build in general way with the opportunity to incorporate different exposure scenarios and sub-scenarios. In this way, scenario-driven exposure assessment may be possible for the heterogeneous group of pesticides. In this context, the complexity of models is ruled by the amount of input parameters, but not by the equations used, or their software-programming. Typical outputs of these models include both aggregate exposures as well as dose of chemicals and its metabolites in blood and or urine.

Table 1: Potential exposure pathways in exposure modeling for pesticides

Inhalation	**Non-dietary**
• Indoor residential air	• Hand to mouth
• Outdoor residential air	• Object to mouth
• Indoor at school/day care	• Hand to object to mouth
• Indoor other	• (Pet contact – (in)direct)
Dietary ingestion (commercial & homegrown)	**Dermal**
• Solid goods	• Hand to hard surfaces
• Liquid goods	• Hand to texture surfaces
• Water	• Clothing
• Beverages	• Pet contact
• Milk	• Other
• Other (Good contacting cont. surfaces)	

Exposure models for pesticides already exist, e.g. CARES[1], Lifeline[2], SHEDS[3]. These computer models are developed for the North American situation and currently subject to evaluation (Rosenheck, 2002 this Report: § III.4.2). In the Netherlands, CONSEXPO[4] is developed at the RIVM (National Institute of Public Health and the Environment) to provide estimation routines for exposure to consumer products, including biocides (Van Veen, 2001)

The model must incorporate potentially relevant exposure pathways for pesticides. Examples of these pathways, grouped by exposure routes are shown in Table 1.

IV.2.3. Modeling at different degree of abstraction, modularization

Exposure assessment can be done at different stages of abstraction, depending on the goal of the assessment. As suggested by different agencies (EPA, 1997; 1998a,b) and others (van Drooge & van Haelst, 2001), a tiered approach is recommended and approved by the working-group as an appropriate approach. General consensus was reached on the necessity of age-dependent modeling. Starting with simple models, you end with sophisticated models and/or human-biomonitoring surveys to get an exposure estimate (Fig. 1).

The exposure **scenarios** and **models** must at least be able to address the reasonable most exposed population (RME) and the average exposure, which includes a cohort approach. It may be necessary to distinguish subgroups with regard to age, sex, social economic status (SES), with regard to regional differences (e.g. in Europe) or to housing types (carpet vs. bare floors, hygiene standard, urban vs. suburban, rented vs. private flats).

IV.2.3.1. Tiered approach

For modeling residential exposure a tiered approach is suggested. In tier 1 a screening level analysis is performed, including all routes and all pathways. If there is reason for concern, a more sophisticated model is needed. The question is, however, how much detail should be included. As a tier 2, a macro approach can be followed, in which e.g. more information on time distribution is included. If there is still reason for concern, further refinement is needed, resulting in a micro approach. In case it is relevant, e.g. when a parameter is dominant, a probabilistic approach is preferred. However, if information on distribution is not available, use of a point estimate is recommended.

IV.2.3.2. Probabilistic modeling

At the screening level (tier I) the use of deterministic modeling techniques is common practice: For each of the model variates single point estimates are used. At higher tiers, probabilistic techniques may be appropriate in order to model the exposure on distribution basis. In contrast to the deterministic approach, full statistical distributions of the model variates are used. Probabilistic modeling offers the opportunity to characterize the variability in exposure estimates. The use of probabilistic techniques in higher tiers of modeling is encouraged by the working group. These techniques offer the opportunity to model the variability of the exposure estimates and provide information about the distribution of

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1 developed by Infoscientific.com

2 developed by Lifeline Group

3 Stochastic Human Exposure and Dose Simulation Model (SHEDS), developed by EPA's Office of Research and Development National Exposure Research Laboratory (see Özkaynak et al., 2002)

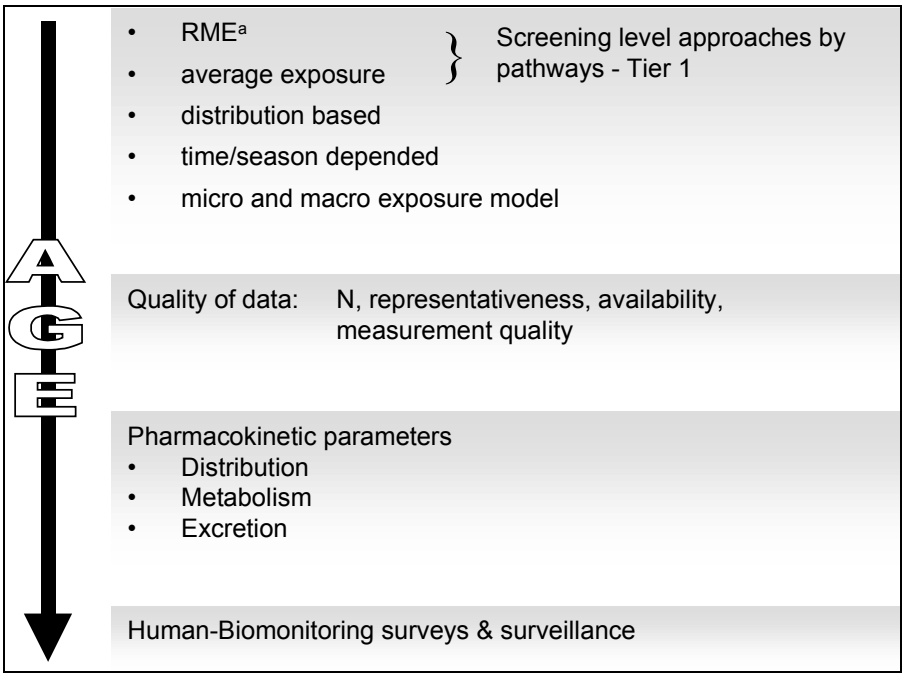
4 CONSumer EXPOsure models

the exposure in the population (Mosbach-Schulz, 2002). Further more, these techniques may also applied for modeling true uncertainty apart from variability (Mekel, 2002). The two dimensional modeling of variability and uncertainty however is not an easy task, more experience is needed.

IV.2.3.3. Age-dependent modeling

With regard to children at least the following age groups should be distinguished: 0-0.5, 0.5- 1, 1-3 and 3-5 years. This differentiation is based on the differences in developmental status, behavioral aspects as well as changes in time- and activity-patterns of children at different ages. Currently, most of the exposure models focus on children at age of 1 year and beyond.

Figure 2: Degree of abstraction, modularisation of exposure models



[a] Reasonable Most Exposed

IV.2.3.4. Data quality

The quality of the data with respect to substances and products, exposure factors and behavior related data, depends on a number of factors, e.g. sample size, representativeness, availability, measurement quality.

Best professional judgement is needed for a lot of exposure variates (input parameters), because data are lacking. E.g. how often a child will enter rooms where pesticides where applicated. Some data may be collected by conducting appropriate studies. Other data may be if at all, obtained by large research programs. However, the data quality will always be subject to professional judgement.

IV.2.3.5. Data availability

Regarding the availability of data for exposure modeling of pesticides, following situations can occur:

- critical data on a product, chemical or exposure scenario non existent
- some data exits, but limited in quality or certain pathways
- some data exits, but proprietory (i.e. not available to most researchers or analysts)
- comprehensive database with variable type and quality.

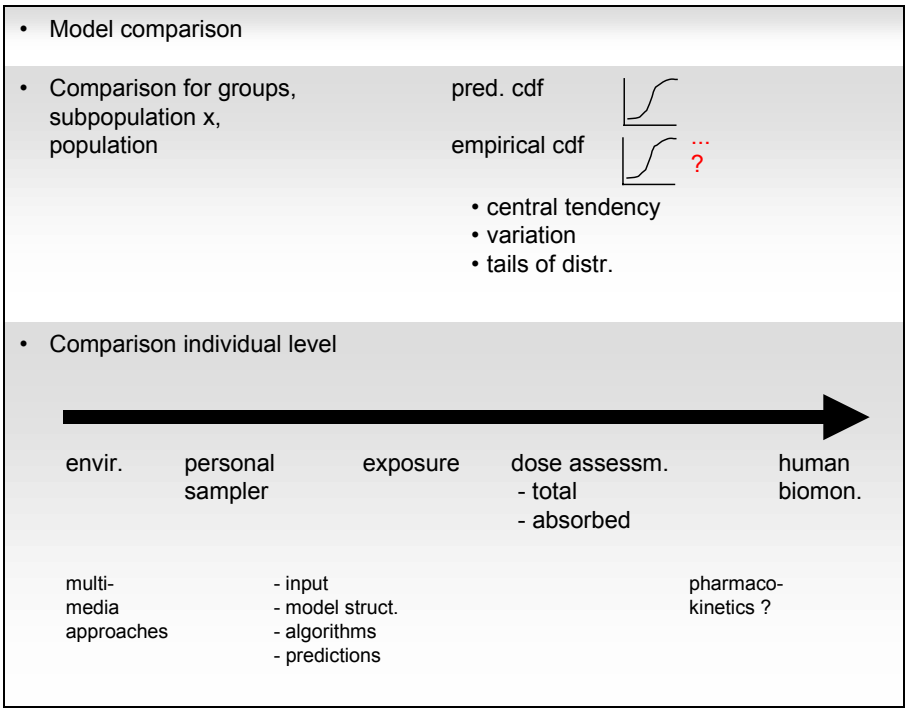
It is recommended to identify critical data needs from Tier I, literature and other assessments, and collect and **share** the data needed with collaborative/consultative research involving private and public sector in **timely** manner.

IV.2.4. Evaluation and validation of exposure models

There is a strong need for evaluation or validation of existing exposure models. Without going into detailed discussion about the differences between validation, calibration and evaluation, the working group feels that efforts need to be made to answer the question 'How can we be more comfortable about the model?'. By doing model comparison, comparison for groups (subpopulations, population) and parameter calibration, a stepwise refinement of the exposure models may be possible. Human biomonitoring may be used for evaluation purposes, but the expectations must not be too high. Human-biomonitoring studies give information about the total absorbed dose. Validation of total absorbed-dose models is complicated resp. difficult, because the models look only at a part of the total exposure. For example, air exposure models may perhaps be ‘validated’ by personal monitoring devices.

Figure 3 illustrates the relation between the different levels of model evaluation and comparison.

Figure 3: Different levels of model evaluation



IV.2.5. Overview on country-specific approaches

IV.2.5.1. The Netherlands

The risk assessment for product registration of pesticides and new chemicals is based on a reasonable worst case scenario (point estimate). For the exposure modeling, fact-sheets on default scenarios and default exposure factors are developed, e.g. for paint use. The exposure model starts from the product or substance.

IV.2.5.2. US EPA

Input of the exposure models for pesticides are field measurements and not necessarily products or substances. US EPA has developed sophisticated models for compounds with a short half-life-time addressing acute exposure situations. EPA follows a tiered approach: tier 1: screening level analysis by exposure pathway. If there is a concern-> tier 2: by pathway.

IV.2.5.3. Sweden

For product registration, no (sophisticated) exposure modeling is done. The evaluation is based on hazard identification. As a part of the evaluation, the new product is compared to existing products on the Swedish market with similar effect (treatment), but with known minimal health effects. The new product/substance must have an extra benefit, otherwise it will not be registered in Sweden.

IV.2.5.4. Germany

Exposure assessment in the context with risk assessment of new and existing chemicals is performed to the rules of the Technical Guidance Documents (TGD, 1996). They are based on a worst case concept very close to the NL-concept. For pesticides, intake rates (accepted daily dose) are deduced from hazard data using safety factors to control exposures from contaminated food. Germany enforces the research for new methodologies of risk assessment, particularly studies of usefulness of approaches that consider variability and uncertainty on the basis of distribution dependent analyses (probabilistic approach). Although pesticide products and, from 2002 biocidal products have to be registered, a nationwide product register is missing.

IV.2.6. Conclusions

There is a strong need to get an overview on which institutions, governments etc. have information about pesticide exposure modeling and bring them together and share there knowledge. The BgVV-workshop is a good start, a follow-up is urgently required.

IV.2.7. References

1 Drooge, van, H.L., van Haelst A.G. (2001): Probabilistic exposure assessment is essential for assessing risks - summary of discussions. Ann Occup Hyg 45, Suppl 1: S159-62.

2 EPA (1997a): Policy for use of probabilistic analysis in risk assessment. Science Policy Council. Washington, D.C.

3 EPA (Environmental Protection Agency) (1998a): Supplemental guidance to RAGS: The use of probabilistic analysis in risk assessment. Part E. Working Draft. February 1998. Office of Solid Waste and Emergency Response.

4 EPA (Environmental Protection Agency) (1998b): Guidance for Submission of Probabilistic Exposure Assessments to the Office of Pesticide Programs. Office of Pesticide Programs, U.S. EPA Washington, D.C.

5 Mekel, O. (2002): Uncertainty and variability of exposure data. This report.

6 Mosbach-Schulz, O. (2002): Deterministic versus probabilistic estimation of exposure? This report

7 National Research Council (1983): Risk Assessment in the Federal Government, Managing the Process. National Academy Press, Washington DC.

8 Özkaynak, H., Zartarian, V., Xue, J., Furtaw, E., Rigas, M. (2002): Modeling exposures to pesticides: Approaches and modeling needs. This report.

9 Rosenheck, L. (2002): Requirements for models used for exposure assessment to pesticides. This report.

10 TGD: Technical guidance document in support of commission directive 93/67/EEC on risk assessment for new notified substances and commission regulation (EC) No 1488/94 on risk assessment for existing substances. Part I, (1996). Office for Official Publications of the European Communities, Luxembourg

11 Van Veen, M.P. (2001): CONSEXPO 3.0, Consumer exposure and uptake models. Report 612810 011, RIVM Bilthoven, The Netherlands (with CD-ROM).

Open Presentation

IV.3. Working group 3: "Residential uses of pesticides"

Topics to be addressed: Identification and characterisation of main pesticide uses in households, direct and indirect uses.

Chairperson: Curt Lunchick

Rapporteur: Lars Neumeister

Co-Rapporteur: Katinka van der Jagt

further working group members: Wolfgang Brehmer, Alex Capleton, Jutta Herrmann, Gabriele Leng, Franz Stauber

Open Presentation

A report of group discussion and preliminary conclusions.

Note: Not included in the group discussions were following exposure sources:

- ambient air and contaminated soil
- food and beverages

IV.3.1. Goal

Preparation of a paper addressing "Residential uses of pesticides" - Identification and characterisation of main pesticide uses in households including professional and homeowner applications as well as indirect uses e.g. treated carpets

IV.3.2. Introduction

Exposure potential of homeowners and professionals are different *during* and *after* an application. There is a clear distinction between an application done by a professional pest control operator (PCO) and an application done by a homeowners.

- Professionals (ideally) wear protective clothing, are trained, apply the appropriate pesticides and amounts and use the correct application equipment.
- Homeowners are mostly not at home while professional applicators treat a home.
- Post application exposure of the homeowner is the major concern in this case!

Application conducted by homeowners are of potential exposure concern since:

- Homeowners typically wear no protective clothing, are not trained, do not handle the application equipment correctly, have difficulty accurately interpreting application rates correctly, and do not minimize drift. Homeowners are directly exposed during treatment but post application exposure of the homeowner and his/her family is of great concern too.

Another distinction must be made regarding indoor and outdoor uses. Pesticide used indoor do not degrade under the influence of UV light and do not leach into the soil or run off after precipitation. They often remain within the house, even if they may circulate with dust and air.

Examples of post-application exposure:

- Dog as exposure source: secondary contact, tertiary contact (etc.) possible by petting the dog, the dog sitting on the couch, house hold dust contaminated by dog
- Lawn as exposure source, also 'track in' (from outdoor to indoor) identified as an important route

- Dermal, inhalation, and oral (children's hand to mouth behaviour) contact following carpet application
- Dermal, inhalation, and oral (children's hand to mouth behaviour) contact following professional or homeowner application via house dust, air
- Inhalation exposure from emenators

IV.3.3. Availability of residential pesticide use and exposure data

The first question addressed by the group was if there are any use data for pesticide use in households available. Industry states that it is hard to obtain these data and that only marginal data are available, as it costs a lot of money and a lot of time to develop. As first steps in accumulating this information the following is suggested:

1. Identify any existing data from EU Member State surveys or from marketing surveys of purchasing patterns, or from sales records of pesticide products.

Thereby recognize differences between consumer products and professional products. Different residue limits and different methods for obtaining the data are necessary to address this issue.

2. Define uses and variables indoor and outdoor that are important with regards to exposure.
3. In addition, focus on efficient data development, as there are limitations on money and manpower.
4. Get use patterns established, as collection of pesticide use information is essential to assessing exposure and risk.

The suggested approach is to begin with the most heavily used scenario to focus the data development. A survey launched in the US indicates that industry's initial focus ‘Lawn and Garden use’ was not the most frequent use category (insect repellents were).

A few questions are:

- Who uses what?
- How is it used?
- When is it used?
- Where is it used?

For setting priorities the following is suggested:

a. Search for and obtain existing data

The use of sales/retail reports is suggested to define and narrow regions of heavy use to guide biomonitoring. User surveys are suggested to define individual habits and patterns. The use of pest control company reporting/data is also encouraged. In addition, existing sources (government required application records, commercial sales data) should be identified and evaluated (e.g. records of professional applicators).

b. Evaluate the data

From the user survey data the use patterns of highest concern could be defined, based on incidence of for example fogging versus bait and frequency data. A pilot and possibly a statistically representative survey of consumer use patterns is needed for use with exposure data for modeling (e.g. REJV survey in U.S. statisticians say for the population

280 million you need 1000 surveys/respondents at a *National* level, for Europe this should be discussed with statisticians, what population needs to be monitored).

From the retail reports the regions of highest concern could be identified from information on the use of certain pesticides. This permits categorising use scenarios, patterns and sources of exposure for development of exposure data collection and product types (also for future scenarios).

c. Identify data gaps

Biomonitoring could potentially be very important to fill in data gaps on exposure.

Recommendation: Set up a pesticide biomonitoring database that can be used to identify the biomonitoring dose range applicable for individual pesticides.

Advantages of biomonitoring:

- Measure the internal dose, gives information on body burden (of also children)
- Provides information on duration of measurable absorbed dose to delineate duration of potential environmental monitoring indoors
- Identifies the magnitude of problem

Disadvantages of biomonitoring:

- No distinction between the different exposure sources
- Potential appearance sensitivities involving the monitoring of people in general and children in particular

First steps to create a pesticide specific biomonitoring database:

1. Priority pesticides and inerts should be identified (not always the pesticide is the problem, sometimes solvents are more of a problem) from feasibility standpoint and what is being used by the consumers and what poses a threat human health. In addition, components which are considered representative (environmental fate, exposure patterns) for classes of components or other components should be chosen.
2. The problem of proprietary versus public data needs to be resolved, it has to be a joined effort of industry, EU and research institutes as central EU reporting should be the goal. Reporting should be on the “chosen few” defined to be representative for future components.
3. Biological monitoring (Urine) provides an important first step in defining the range of absorbed doses of pesticide active ingredients or their metabolites and inerts or their metabolites in the EU population. Data need to be collected and entered in a database.

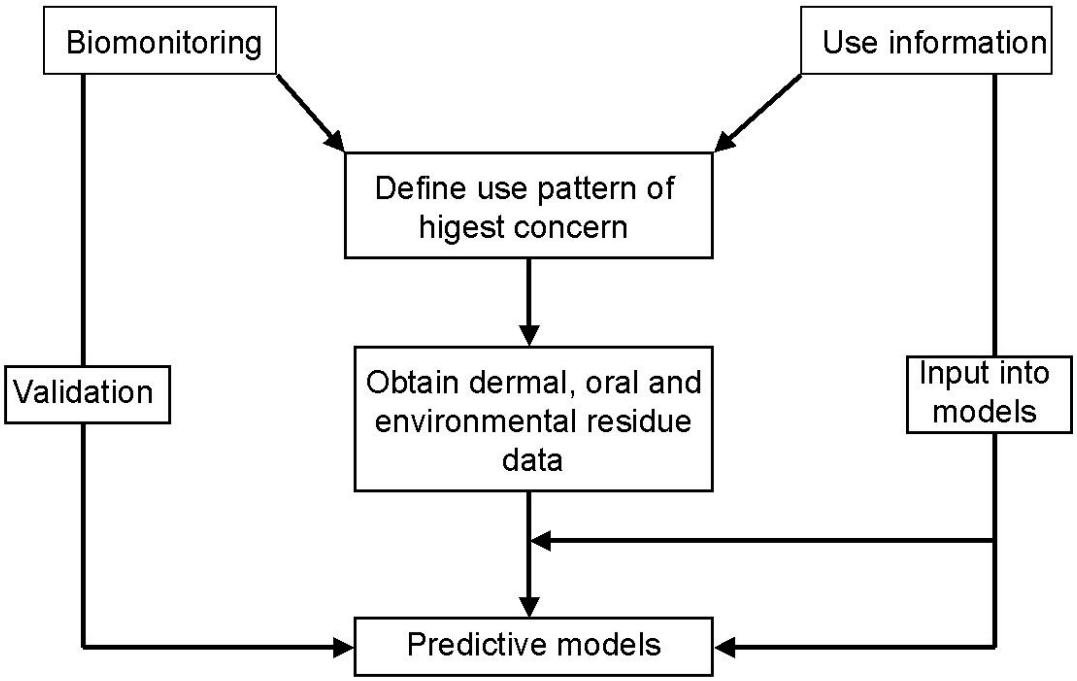
Specifics regarding approaches, study designs, reference rates, data sharing should be addressed in the near future by an additional working group.

d. Use the above points to set (new) priorities and/or develop additional data.

e. Use conclusions to guide development of additional data

IV.3.4. Conclusion

The following road map is recommended for addressing consumer exposure.



In order to focus research, existing biomonitoring data and pesticide use data (retail and/or survey data) are utilised to define use patterns and regions of high concern. Targeted monitoring then delivers dermal, inhalation, oral and environmental residue data. All data go after validation into models to predict exposure.

Application of the data in probabilistic models could be another procedure to estimate exposure.

Open Presentation

IV.4. Working group 4: Behavior of children as a factor determining exposure

Chairperson: **Steve Olin**

Rapporteur: **Bea Steenbekkers**

Co-Rapporteur: **Natalie Freeman**

Working group members: Martha Harnly, Olaf Mosbach-Schulz, Emanuele Pydde, Thomas Rüdiger, Bettina Schmidt-Faber, Bärbel Vieth

The charge to the Working Group was to consider the behaviors of children that lead to typical exposures to pesticides. This includes those behaviors that differentiate children from adults (e.g., breast feeding, crawling, mouthing) and also children's time budgets (i.e., frequency and duration of behaviors that may lead to exposures).

A partial bibliography of pertinent references is included as Section II.4.5.

IV.4.1. Introduction

The statement that "children are not little adults" has become the mantra for research into children's exposure to environmental contaminants. Children differ from adults in their activity patterns, where they spend time, how long they spend time in various environments, and in the types of microactivities in which they engage. One can go further and state that infants are not toddlers who, in turn, are not the same as school-aged children or adolescents. It is necessary to characterize the behaviors of each subcategory of children and how these behaviors may uniquely expose them to pesticides.

IV.4.2. Children as a population

In evaluating behaviors contributing to children's exposure to contaminants, several parameters need to be kept in mind. These include the prevalence and frequency of the behaviors, whether the behaviors are age dependent, how long the behaviors occur as individual events, and the duration of occurrence of multiple events during the life of the child. In addition, variations in behaviors and their occurrences, and the resultant exposure to environmental contaminants, may be influenced by regional, cultural, temporal, and birth order factors.

IV.4.2.1. Discrimination of specific age categories

- *Which age groups should be addressed for exposure assessment?*

Based upon discussions at a workshop in July 2000, the US EPA has drafted a minimum set of 10 childhood age categories for exposure assessment. The breakdown includes 5 "fine" subdivisions for children less than 12 months old. These "fine" subdivisions, prenatal, neonatal less than 1 month, early infancy, mid infancy, late infancy, are less a result of differences in the behaviors of the children in these age groups than of anatomical, physiological and functional changes occurring during the first year of life.

Other options for creating age categories might be dietary habits (nursing, baby food, adult food limited variability, and adult food adult type variability) and activity patterns (mobility, mouthing habits, hygiene).

Dietary habits have an important influence on children's exposure to pesticides. During the nursing period, the child is exposed primarily to pesticides in the water compartment of milk, or pesticides in the fat compartment that have been mobilized from the mother's fat stores. Commercially available baby food in some countries is strictly monitored for pesticides and hence is less likely to be a source of exposure for the child. In contrast, some adult foods may have measurable pesticides. When the child starts eating adult food, the range in diet tends to be limited, and the child may be more exposed to some pesticides than if the child ate a wider range of foods.

Activity patterns of the child may influence where and to what extent the child is exposed to pesticides. Infants mouth a great deal, particularly while teething, yet their lack of mobility limits their access to dusts and soils that contain contaminants. Young toddlers still exhibit mouthing behavior and their greater mobility increases their potential exposure. Several time/activity studies are available (Germany, US-NHAPS, US-NHEXAS, US- California Air Resources Board). There are, however, few data available on the time/activity patterns of very young children.

- *Are there characteristic exposures for specific age groups of children?*

Exposures to children other than toddlers have not been studied systematically, so that it is unclear if there are characteristic exposures related to age groups other than toddlers. For toddlers, both mouthing behaviors and limited diets of adult foods have increased their exposures to some pesticides. The lack of data on other age groups means that we do not know if these same behaviors contribute to exposure, or whether there are other age-specific contributors to exposure.

IV.4.2.2. Influence of other persons (e.g., parents) on children's exposure

- *Breast feeding*

There are good data on most exposure parameters related to breast feeding in Germany, as well as in the US and some other countries. What is needed is information about levels of contaminants in breast milk, and information about variations in breast feeding habits across countries, and cultures, and variations in contaminants across countries and cultures. The critical importance of exposures by this route is in the first 6 –12 months of life, depending on duration of breast feeding.

- *Processed foods*

There is good information on pesticide levels in German baby food that is commercially processed. Levels in adult foods fed to children are known to the extent that they are monitored in individual countries. Food intake habits need to be studied. In Germany, the Dortmund study of children 0-5 years of age is expected to be available by 2003. The World Health Organization collects data on world regional diets. In the US, the National Health and Nutrition Evaluation Survey (NHANES) conducted by the CDC monitors a population-based sample of adults and children and has some information about dietary habits. In addition the US Continuing Survey of Food Intake of Individuals (CSFII) provides population-based information about people's eating habits. While these databases are interesting and useful for some purposes, it is unclear whether one can extrapolate from country to country or between cultural groups.

What is still needed is longitudinal data to understand the eating habits of individuals. Most dietary studies do not follow individuals through a year but only collect data for one or two days. Estimates of pesticides in diets are typically calculated from market basket

surveys or agricultural products. Combined duplicate diet studies with biomonitoring are needed to compare and evaluate the reliability of pesticide dietary exposure estimates made by these other methods.

- *Other factors (e.g., pets, toys, parental occupation, parental habits at home)*

Children may become exposed to pesticides from the clothes that their parents wear at work and bring home with them. In addition, parent use or abuse of pesticides in the home may lead to inadvertent contamination of food, food preparation areas, toys, and bedding. Contact between children and their pets is variable. Depending on the type of pesticide treatment of the pet, children may or may not be exposed to pesticides from this source. In addition, pets that play on treated carpets or lawns may become vehicles for exposing children. Behaviors of parents may also change the environmental conditions within a home, such as replacing carpeting or repainting walls. Replacement of carpet may have two effects, disturbing the pesticides which are in the dust within and below the carpet, and introducing new pesticides if the carpet has been treated with fungicides or miticides. New paints may also contain fungicides which will off-gas for some period of time.

IV.4.2.3. Influence of the child on his/her exposures

Activities in daily life

- *Children at play (contact with soil, dust, etc)*

Both dust and soil are potential sources of exposure to children who play on floors and carpets, or outdoors. Dust may actually have higher contaminant levels than soil since some pesticides degrade in sunlight, and therefore would degrade less readily indoors (example: chlorpyrifos).

Critical research areas for dust and soil as sources are how much actual exposure occurs (dermal, oral) and in what circumstances (urban/suburban/rural, cleaning habits, pesticide use patterns in and around the home).

- *Eating (contamination of food)*

Contamination of food by children has been documented for lead and metals found in house dust. Similar studies have not been done for pesticide exposure. At the same time, hand wipes and hand rinses have documented that children may be exposed to a range of pesticides which could be transferred to food when eaten by hand.

- *Sucking (mouthing behavior)*

There are presently three small studies of mouthing behaviors in the literature (NL-Steenbekkers, US-Zartarian, US-Reed). Others are in progress (US-CPSC and US-Rio Bravo). In order to characterize behavioral influences on exposure, this information must be combined with knowledge of time/activity patterns (where children spend time) and contamination levels in those locations.

- *Regional factors influencing exposures (e.g., urban vs. rural)*

Differences in activity patterns between children in urban and rural settings and their effect on exposures have not been studied systematically. Some differences in activity patterns probably exist between countries and geographic regions as well, but data are lacking.

- *Children's exposure as a result of staying at specific places (home, day care, farms, etc.)*

Other sources of exposure for children may be related to the specific places where children live such as farms, or near to industrial sites. A few studies are available. Little is known about the presence of residual pesticides in day care and nursery school environments, or how these institutions are treated to control pests.

IV.4.3. Conclusions

The behaviors that contribute significantly to a child's exposure will depend upon the type of pesticide as well as the age of the child. For example:

a. With regard to volatile fumigants used in homes, a child's level of physical activity and respiration rate (relative to the number of alveoli) may be most important. Air levels of pesticides also may be important for other selected pesticides and formulations, or for specific applications designed to generate aerosols.

b. In contrast, for pesticides occurring in foods, food residue levels and dietary habits will be most important when assessing dietary ingestion.

c. Dermal contact with surfaces and mouthing behaviors may be most important for semi-volatile pesticides and pesticides distributed in particle forms. Again, both the behavior and the formulation are important, as well as the persistence of the pesticide after application.

d. There are many significant data gaps and research needs for an adequate understanding of the effects of behavior on children's exposures to pesticides, as noted in the paragraphs above. In particular, major studies are needed to characterize:

    - Time budgets and activity patterns (macro and micro) of children in different age categories
    - Longitudinal eating patterns and habits of individuals
    - Adult behaviors that influence children's exposures

More biomonitoring data on children's exposures would allow correlation with behavior patterns and validation of estimates from modeling.

IV.4.4. References

1. Adair, J.H. and Spengler, J.D. Assessing activity patterns for air pollution exposure research, in T.H. Starks (ed.) Research Planning Conference on Human Activity Patterns. U.S. Environmental Protection Agency (EPA-600/4-89-004) Las Vegas. 1989: pp. 6-1 to 6-19.

2. Baas, M.B.M., Steenbekkers, L.P.A. and van Veen, M.P., Residential use of biocide sprays, Proceedings of the international conference 'Changes at the other end of the chain', in press.

3. Bayley, N. Individual patterns of development," pp. 417-426 in: Jones et al. (eds.) The Course of Human Development. Waltham MA: Xerox College Pubs. 1971.

4. Bjorklund, D.F. and Brown, R.D. Physical play and cognitive development: Integrating activity cognition, and education. Child Devel. 1998: 69: 604-606.

5. Buss, D.M., Block, J.H. and Block,J. Preschool activity level: Personality correlates and developmental implications. Child Devel. 1980: 51: 401-408.

6. Byers, J.A. The biology of human play. Child Devel. 1998: 3: 599-600.

7. Bradman MA, Hearnly ME, Draper W, Seidel S, Teran S, Wakeham D, Neutra R. Pesticide exposures to children from California's Central Valley: results of a pilot study. J Exp Anal Environ Epidemiol 7:217-234 (1997).

8. Carlstein, T. Time Resources, Society and Ecology. George Allen & Unwin, London. 1982.

9. Carlstein, T. and Thrift, N. Afterword: towards a time-space structured approach to society and environment, in: T. Carlstein, et al. (eds.) Human Activity and Time Geography. John Wiley & Sons, New York. 1978: pp. 225-263.

10. Chapin Jr., F.S. Activity analysis, in: Whittick, A. (ed.). Encyclopedia of Urban Planning. McGraw-Hill Book Co., New York. 1974a: pp. 5-8.

11. Chapin Jr., F.S. Human Activity Patterns in the City. John Wiley & Sons, New York. 1974b.

12. Chapin Jr., F.S. Human time allocation in the city, in: T. Carlstein, et al. (eds.). Human Activity and Time Geography. John Wiley & Sons, New York. 1978: pp. 13-26.

13. Cohen-Hubal, E.A., Sheldon, L.S., Burke, J.M., McCurdy, T.R., Berry, M.R., Rigas, M.L., and Zartarian, V.G. Children's exposure assessment: A review of factors influencing children's exposure, and the data available to characterize and assess that exposure. Environ. Health Persp. 2000:108: 475-486.

14. Davis JR, Brownson RC, Garcia R. Family pesticide use in the home, garden, orchard, and yard. Arch Environ Contam Toxicol 22:260-266 (1992).

15. Eaton, W.O. and Yu, A.P. Are sex differences in child motor activity level a function of sex differences in maturational status? Child Devel. 1989: 60: 1005-1011.

16. Echols, S.L., MacIntosh, D.L., Hammerstrom, K.A., and Ryan, P.B. Temporal variability of microenvironmental time budgets in Maryland. J. Exp. Anal. Environ. Epidem. 1999: 9: 502-512.

17. Fales, E. A rating scale of the vigorousness of play activities of preschool children. Child Devel. 1938: 8: 15-46.

18. Fenske RA, Black KG, Elkner KP, Lee CL, Methner MM, Soto R. Potential exposure and health risks of infants following indoor residential pesticide application. Am J Public Health 80:689-693 (1990).

19. Fenske RA, Kissel JC, Lu C, Kalman DA, Simcox NJ, Allen EH, Keifer MC. Biologically based pesticide dose estimates for children in an agricultural community. Environ Health Perspect 108:515-520 (2000)

20. Freedson, P.S. Field monitoring of physical activity in children. Pediatr. Exer. Sci. 1989: 1: 8-18.

21. Freedson, P.S. Electronic motion sensors and heart rate as measures of physical activity in children. J. School Health. 1991: 61: 215-219.

22. Freeman, N.C.G., Jimenez, M., Reed, K.J., Gurunathan, S., Edwards, R., Roy, A., Adgate, J., Pellizzari, E.D., Quackenboss, J., Sexton, K., and Lioy, P.J. (2001) Quantitative analysis of children's activity patterns of children: The Minnesota Children's Pesticide Exposure Study. Journal of Exposure Analysis and Environmental Epidemiology in press.

23. Freeman, NCG, Sheldon, L, Jimenez, M, Melnyk, L, Pellizzari, E, and Berry, M. (2001) Contribution of children's activities to lead contamination of food. Journal of Exposure Analysis and Environmental Epidemiology. 11: 407-413.

24. Freeman, N.C.G., Ettinger, A., Berry, M., and Rhoads, G. (1997) Association of hygiene and food related behaviors with blood lead levels of young children from lead contaminated homes. Journal of Exposure Analysis and Environmental Epidemiology 7: 103-118.

25. Freeman, N.C.G. and Lioy, P.J. Responses to Region V NHEXAS time/activity diary. J. Exp. Anal. Environ. Epidem. 1999: 9: 414-426.

26. Groot, M.E., Lekkerkerk, M.C., and Steenbekkers, L.P.A.. Mouthing behaviour of young children: an observational study. Agricultural University, Wageningen. Wageningen, The Netherlands. 1998.

27. Gurunathan S, Robson M, Freeman NC, Buckely B, Roy A, Mayor R, Bukowski j, Lioy PJ. Accumulation of chlorpyrifos on residential surface and on/in toys accessible to children. Environ Health Perspect 106:9-16 (1998).

28. Guzelian P.S., Henry C.J., and Olin, S.S. (eds) Similarities and Differences Between

29. Children and Adults: Implications for Risk Assessment. ILSI Press, Washington, DC. 1992.

30. Honzik, M.P. and McKee, J.P. The sex difference in thumb-sucking, pp. 179-182 in: Jones et al. (ed). The Course of Human Development. 1971.

31. Jenkins, P.L., Phillips, T.J., Mulberg, E.J., and Hui, S.P. Activity patterns of Californians: Use of and proximity to indoor pollutant sources. Atmos. Environ. 1992: 26A: 2141-2148.

32. Johnson, T. A Study of Personal Exposure to Carbon Monoxide in Denver, Colorado. Research Triangle Park NC: U.S. Environmental Protection Agency (EPA 600/S4-84-014). 1984.

33. Johnson, T. Human Activity Patterns in Cincinnati, Ohio. Electric Power Research Institute, Palo Alto CA. 1989.

34. Jones, M.C., Bayley, N., Macfarlane, J.W., and Honzik, M.P. The Course of Human Development. Waltham MA: Xerox College Publishing. 1971.

35. Juberg, D.R., Alfano, K., Coughlin, R.J., Thompson, K.M. "An observational study of object mouthing behavior by young children." Pediatrics 2001: 107: 135-142.

36. Kalkwarf, H.J., Haas, J.D., Belko, A.Z., Roach, R.C., and Roe, D.A. Accuracy of heart-rate monitoring and activity diaries for estimating energy expenditure. Amer. J. Clin. Nutr. 1989: 49: 37-43.

37. Klepeis, N., Tsang, A., and Behar, J.V. Analysis of the National Human Activity Pattern Survey (NHAPS) Respondents from a Standpoint of Exposure Assessment. National Exposure Research Laboratory, U.S. Environmental Protection Agency, Las Vegas NV. 1995.

38. Loewenherz C, Fenske RA, Simcox NJ, Bellamy G, Kalman D. Biological monitoring of organo-phosphorous pesticide exposure among children of agricultural workers in Central Washington State. Environ Health Perspect 105:1344-1353 (1997).

39. Lu C, Fenske RA, Simcox NJ, Kalman D. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. Environ Res 84:290-302 (2000).

40. Lu C, Fenske RA Dermal transfer of chlorpyrifos residues from residential surfaces: comparison of hand press, hand drag, wipe, and polyurethane foam roller measurements after broadcast and aerosol pesticide applications. Environ Health Perspect 107:463-467 (1999).

41. Maffeis, C., Zaffanello, M., Pinelli, L., and Schutz, Y. Total energy expenditure and patterns of activity in 8-10-year-old obese and nonobese children." J. Pediatr. Gast. Nutr. 1996: 23: 256-261.

42. McCurdy, T., Glen, G., Smith, L., and Lakkadi, Y. The National Exposure Research Laboratory's Consolidated Human Activity Database. J. Exp. Anal. Environ. Epidem. 2000: 10: 566-578.

43. McCauley LA, Lasrev MR, Higgins G, Rothlein J, Muniz J, Ebbert C, Phillips J. Work characteristics and pesticide exposures among migrant agricultural families: a community-based research approach. Environ Health Perspect 109:533-538 (2001).

44. Melnyk, L.J., Berry, M.R., Sheldon, L.S., Freeman, N.C.G., Pellizzari, E.D., and Kinman, R.N. (2000) Dietary exposure of children in lead-loden environments. J. Exposure Analysis and Environmental Epidemiology. 10: 723-731.

45. U.S. Environmental Protection Agency. Child-specific Exposure Factors Handbook. NCEA-W-0853 June 2000 External Review Draft. http://cfpub.epa.gov/ncea/cfm/efcsefh2.cfm

46. O'Rourke MK, Lizardi PS, Rogan SP, Freeman NC, Aguirre A, Saint CG. Pesticide exposure and creatinine variation among young children. J Exp Anal Environ Epidemiol 10:673-681 (2000).

47. Ott, W.R. Human activity patterns: a review of the literature for estimating time spent indoors, outdoors, and in transit, in: T.H. Starks, (ed.) Proceedings of the Research Planning Conference on Human Activity Patterns. U.S. Environmental Protection Agency (EPA-450/4-89-004), Las Vegas. 1989: pp. 3-1 to 3-38.

48. Ott, W.R., Thomas, J., Mage, D., and Wallace, L. Validation of the Simulation of Human Activity and Pollutant Exposure (SHAPE) Model using paired days from the Denver, CO, carbon monoxide field study. Atmos. Environ. 1988: 22: 2101-2113.

49. Ottensman, J.R. Systems of Urban Activities and Time: An Interpretative Review of the Literature. NC: Center for Urban and Regional Studies; University of North Carolina, Chapel Hill NC. 1972.

50. Pratt, M., Macera, C.A., and Blanton, C. Levels of physical activity and inactivity in children and adults in the United States: Current evidence and research items. Med. Sci. Sports Exer. 1999: 31 (Supp.): S526-S533.

51. Que Hee, S.S., Peace, B., Clark, C.S., Boyle, J.R., Bornschein, R.L., and Hammond, P.B. (1985). Evolution of efficient methods to sample lead sources, such as house dust and hand dust, in the homes of children. Environ. Res. 38: 77-95.

52. Reed, K.J., Jimenez, M., Freeman, N.C.G., and Lioy, P.J. Quantification of children's hand and mouthing activities through a videotaping methodology." J. Exp. Anal. Environ. Epidem. 1999: 9: 513-520.

53. Robertson, G.L., Lebowitz, M.D., O'Rourke, M.K., Gordon, S., and Moschandreas, D. National Human Exposure Assessment Survey (NHEXAS) study in Arizoniz–Introduction and preliminary results. J. Exp. Anal. Environ. Epidem. 1999: 9: 427-434.

54. Robinson, J.P. How Americans Use Time. New York: Praeger Publishers, New York. 1977.

55. Robinson, J.P. Time-diary research and human exposure assessment: some methodological considerations. Atmos. Environ. 1988. 22: 2085-2092.

56. Robinson, J.P. and Thomas, J. Time Spent in Activities, Locations, and Microenvironments. U.S. Environmental Protection Agency (EPA-600/4-91-006), Las Vegas. 1991.

57. Robinson, J.P., Wiley, J.A., Piazza, T., Garrett, K., and Cirksena, K. Activity Patterns of California Residents and Their Implications for Potential Exposure to Pollution. Sacramento CA: California Air Resources Board (CARB-A6-177-33), Sacramento. 1989.

58. Roth Associates A Study of Activity Patterns Among a Group of Los Angeles Asthmatics. Palo Alto CA: Electric Power Research Institute. 1988.

59. Roth Associates A Survey of Daily Asthmatic Activity Patterns in Cincinnati. Palo Alto CA: Electric Power Research Institute. 1989.

60. Ruff, H.A. Infants' manipulative exploration of objects: Effects of age and object characteristics. Devel. Psychol. 1984: 20: 9-20.

61. Ruff, H.A. and Dubiner, K.. Stability of individual differences in infants' manipulation and exploration of objects. Percep. Motor Skills 1987: 64: 1095-1101.

62. Savage EP, Keefe TJ, Wheeler HW, Mounce L, Halwic L, Applehans F, Goes E, Goes T, Mihlan G, Rench J, Taylor DK. Household pesticide usage in the United States. Arch Environ. Health 36:304-309 (1981).

63. Sayre, J.W., Charney, E., Vostal, J., and Pless, I.B. (1974). House and hand dust as a potential source of childhood lead exposure. Amer. J. Dis. Child. 127: 167-170.

64. Schwab, M., McDermott, A., and Spengler, J.D. Using longitudinal data to understand children's activity patterns in an exposure context: Data from the Kanawha County health study. Environ. Inter. 1992: 18: 173-189.

65. Schwab, M., Spengler, J.D., and Özkaynak, H. Using longitudinal data to understand children's activity patterns in an exposure context, in: Indoor Air '90. Vol. 3. 1990b: pp. 471-476.

66. Shealy DB, Barr JR, Ashley DL, Patterson DG Jr., Camann DE, Bond AE. Correlation of environmental carbaryl measurements with serum and urinary 1-napthol measurements in a farmer applicator and his family. Environ Health Perspect 105:510-513 (1997).

67. Simcox NJ, Fenske RA, Wolz SA, Lee IC, Kalman DA. Pesticides in household dust and soil: exposure pathways for children of agricultural families. Environmental Health Perspectives 103:1126-1134 (1995).

68. Steenbekkers, L.P.A., Methods to study everyday use of products in households: the Wageningen mouthing study as an example, Ann.occup.Hyg. Vol. 45, No. 1001, pp. S125-S129 (2001).

69. Sumner D, Langley R. Pediatric pesticide poisoning in the Carolinas: an evaluation of the trends and proposal to reduce the incidence. Vet Human Toxicol 42:101-103 (2000).

70. Tsang, A.M. and Klepeis, N.E. Descriptive Statistics Tables from a Detailed Analysis of the National Human Activity Pattern Survey (NHAPS) Data. U.S. Environmental Protection Agency (EPA/600/R-96/148), Las Vegas. 1996.

71. Touwen, B.C.L., Hempel, M.S., and Westra, L.C. “The development of crawling between 18 months and four years. Devel. Med. Child Neurol. 1992: 34: 410-416.

72. US Environmental Protection Agency. Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children. EPA/630/R-00/005. December 2000.

73. Vadarevu, R.V. and Stopher, P.R. “Household activities, life cycle, and role allocation.” Transport. Res. Rec. 1556: 77-85. 1996.

74. Vandell, D.L. and Powers, C.P. “Day care quality and children’s free play activities.” Amer. J. Orthopsychiat. 53: 493-500. 1983.

75. Watt, J., Thorton, I., and Cotter-Howells, J. (1993). Physical evidence suggesting the transfer of soil Pb into young children via hand-to-mouth activity. Appl. Geochem.. Supp. 2: 269-272.

76. Whitemore RW, Immerman FW, Camann DE, Bond AE, Lewis RG, Schaum JL. Non-occupational exposures to pesticides for residents of two U.S. Cities. Arch Environ Contam Tox 26:47-59 (1994).

77. Wiley, J.A., Robinson, J.P., Cheng, Y.-T., Piazza, T., Stork, L., and Pladsen, K. Study of Children's Activity Patterns. Survey Research Center, University of California, Berkeley CA. 1991a.

78. Wiley, J.A., Robinson, J.P., Piazza, T., Garrett, K., Cirksena, K., Cheng, Y.-T., and Martin, G. Activity Patterns of California Residents. Survey Research Center, University of California, Berkeley CA. 1991b.

79. van Wijnen JH, Clausing P, Brunekreef B. Estimated soil ingestion by children. Environ Res 51:147-162 (1990).

80. Zartarian, V.G., Ferguson, A.C., and Leckie, J.O. Quantified dermal activity data from a four-child pilot field study. J. Exp. Anal. Environ. Epidem. 1997a: 7: 543-552.

81. Zartarian, V.G., Ferguson, A.C., and Leckie, J.O. Quantified mouthing activity data from a four-child pilot field study. J. Exp. Anal. Environ. Epidem. 1998: 8: 543-554.

82. Zartarian, V.G. and Leckie, J.O. Dermal exposure: the missing link. Environ. Sci. Tech. 1998: 32: 134A-137A.

83. Zartarian V.G., Özkaynak H., Burke J.M., Zufall M.J., Rigas M.L., and Furtaw Jr. E.J., “A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and non-dietary ingestion.” Environ. Health Persp. 2001: 108: 505-514.

84. Zartarian, V.G., Streiker, J., Rivera, A., Cornejo, C.S., Molina, S., Valadez, O.F., and Leckie, J.O. A pilot study to collect micro-activity data of two- to four-year-old farm labor children in Salinas Valley, California. J. Exp. Anal. Environ. Epidem. 1995: 5: 21-34.

V. Conclusion: What are the most important factors that limit exposure of children (to be discussed in the plenum. Each working group should provide a short statement)

Gerhard Heinemeyer

V.1. Age groups that should be considered for exposure estimation in childhood.

Since the development of children does not occur linearily, it is important to characterize some ages which can be referred to some developmental stages.

Table 1 shows the main categories of age that should be considered for exposure estimation which has been proposed by the working group 1.

Age category	**age**	
Premature infant	< 36 weeks	
Newborn	1 – < 29 days	
Infant	29 days - < 1 year	
small child	1 - < 6 years	
	1 – <3 years 3 - < 6 years	Due to proposals made by working group II, compare chapter IV.2.3.3
school child	6 - < 14 years	
Adolescent	14 - < 18 years	
Adult	18 - < 65 years	**Table 1: Age categories proposed for estimation of exposure in children vs. adults**
Senior	>65 years	

The table of age categories is extensively characterised in chapter V. As a result of the workshop, however, it seems appropriate to add a subcategory "toddler, 1-3 years" in order to consider the uptake of dust during this period of development.

V.2. The most important source of exposure to children (shown with the example “pesticides”

<u>Use of products in the home</u>

- *Children as bystanders of the use of household and leisure products*

  Normally, children do not use consumer products leading to direct exposure. They are, however, often bystanders which means that an indirect exposure takes place. In general, this indirect exposure scenario is similar to that for adults. Mostly, bystander exposure is by inhalation.

Contaminations, either from consumer- or other uses

- *Soil*

  The scenario of exposure from contamination of soil is typical for children who are playing on the ground e.g. in sandboxes. Children may eat soil, or they can be exposed by hand-to-mouth contact. Contact with soil occurs normally outside and applies to children in the age of one year up to shool ages.

  The uptake of dust and soil has been studied by several authors. In the AUH-report, data from Calabrese have been proposed to be used for estimations of dust exposure.

  Table 2: Uptake of soil, most probable case (data from Calabrese, compare chapter III)

age (y)	< 1	1-3	4-6	7-9	10-14	15-19	20-75
Uptake of soil (mg/d)	20-100	20-100	20-100	5-25	5-25	2-10	2-10

- *Dust*

  This scenario is very similar to contamination of soil. Exposure, however occurs inside the homes, and sust may by contaminated to higher amounts than soil. Exposure to dust applies for all ages, but particularly for little children (infants, toddlers) crawling on the ground. Exposure occurs primarily by hand-to-mouth contact.

Food

- Food may be contaminated with substances e.g. pesticides and may contribute significantly to exposure of children.

Animals

- pets may be treated with chemicals for care and for preventing illness or pest.

  Children often embrace the pets living in their homes which can lead to substantial exposures, particularly pesticides. Similar scenarios may apply for textiles that are treated with chemicals against pest and where children are playing.

V.3. Important paths of exposure to children?

V.3.1. Oral

- *hand-to mouth-contact*

  As stated above, the hand-to-mouth contact plays a predominant role for exposure of children. This has been discribed in the contribution of B. Steenbekkers (chapter II.1.3) and by working group IV (chapter IV.4)

- *food*

  Different eating habits of children vs. adults should be taken into consideration. Hovewer, the influence of eating with regard to age groups in children is not well documented.

- *sucking, biting*

  This typical habits of children may lead to oral exposure to substances. It applies for those chemicals that are migrating from articles, in particular toys and other articles (dummies, suckers) and any other things children put into the mouth.

V.3.2. Dermal

- Contact of skin to contaminated soil due to crawling and playing on the ground is more frequent than in adults. This applies for soil (outside) and for dust (inside). It is anticipated that the substances which are transferred by these carriers are mostly those that are not volatile.
- Due to the relative higher body surface of children the absorbed dose is higher than in adults when referred to bodyweight.

V.3.3. Inhalation

- Because children and adults inhale the same substance concentration there is in principle no difference between children and adults of ihalation exposure. The models used to not considere possible physiological differences between children and adults. They only consider the breathing volumes which must not reflect the real situation. Other models that consider lung surface and a gradient through the lung wall which has been described by Fick for the absorption of oxygen could be helpful for building mor precise models of lung absorption.

V.4. How do children differ from adults?

V.4.1. Toxicokinetics

There are important differences in toxicokinetics between children and adults. This is figured out in chapters II.1.1, II.5.13, and IV.1. In general, the clearance changes during childhood. From evaluations of drug kinetics, we know that in newborns the clearance is lower, and, in the age between 1 and 6 years it is higher than in adults. This is due to the higher capacity of metabolism and to changes in the volumes of distribution. For toxicokinetic evaluations, this can mean, that toxic doses may be higher in children than in adults. Vice versa, if toxic metabolites are formed, this can lead to higher toxicity.

V.4.2. Toxicodynamics

Developmental changes during childhood are of great importance. As figured out in chapters II.1.1 and III, the different organ systems are developing differently in children, which must be considered. The consequence is that e.g. substances affecting the endocrine system may be relative untoxic during the first years of life, but neurotoxic substances may lead to desastrous effects during this period. Taking these points into account, the toxic properties in of substances for children must be related to the development.

V.4.3. Anthropometrics

Children are no little adults. Effects that have been shown in adults cannot be extrapolated to children without some caution. There is no linear relationship between age and bodyweight. It has been shown that there is good correlation of body functions e.g. basal metabolism with body surface. For instance, dosage of drugs in childhood can better be correlated to body surface than to bodyweight.

Body surface can be easily calculated by the formula $BS = 0{,}0239 * H^{0{,}417} * W^{0{,}517}$.

For comparisons of data between children and adults, it seems therefor more appropriate to take to refer to bodysurface than to bodyweight.

Similar considerations have been made for lung function. In the existing approaches, only the breathing volume is used to estimate the exposure from inhalation. This concept, however, does not consider that there should be a steady state concentration between in- and outside the lung, the dead-volume is unconsidered and the lung respiratory minute ventilation rate per square meter of lung surfact area is 40-fold to 60-fold greater in children than adults.

Age	Body weight (kg)	Body height (cm)	Body surface (m^2)
newborn	3,27	50,50	0,226
0,25	5,80	60,35	0,328
0,5	7,63	67,68	0,396
0,75	8,63	71,84	0,433
1	9,44	75,07	0,462
1,5	10,80	81,22	0,512
2	12,06	86,14	0,555
2,5	13,26	90,85	0,596
3	14,40	94,95	0,634
3,5	15,38	99,03	0,667
4	16,66	103,20	0,707
5	18,86	110,41	0,776
6	21,16	117,05	0,844
7	23,91	123,42	0,919
8	26,46	128,72	0,985

Age	Body weight (kg)	Body height (cm)	Body surface
10	33,00	140,22	1,145
12	41,51	151,85	1,332
14	52,20	163,35	1,546
16	60,22	169,85	1,692
18	63,39	171,53	1,745
19	63,56	171,54	1,747
20-25	65,65	171,53	1,777
25-30	68,28	170,13	1,807
30-35	69,81	168,92	1,822
35-40	70,42	167,74	1,825
40-45	72,20	168,04	1,850
45-50	73,15	166,24	1,855
50-55	74,07	165,12	1,861
55-60	72,52	164,45	1,838

Table 3: Body weights, -heights, and -surfaces of humans in different ages (data taken from AUH-report), male and female. Body surface has been calculated by the above mentioned formula.

V.4.4. Behaviour

The behaviour of children is one of the factors influencing their own exposure is highly uncertain. It is, however, believed that it plays an important role. Children may influence their exposure by some activities which are different to adults.

First of all, the time staying at home may be different to adults, but changes with age. This may be of importance for dicrimination of exposure in very young children and e.g. school-children and is reflected in table 1.

Secondly, exposure in children may be ruled by their microactivities. The most important activities that should be considered for estimation of exposure are:

1. Crawling on the floor. This applies to children in the early ages. Exposure occurs indoors to substances which are migrating from articles, furniture and other fixtures as well as from impregnations.

2. Playing on the ground. This applies for all children. Exposure occurs during playing inside and outside.
3. Playing with pets. Occurs by playing with pets which are e.g. treated with agents against flies and fleas.
4. Playing with food. Contaminations of hands may lead to oral exposure during eating. Some children extensively play with their food.
5. As a specific pathway for very young children, the uptake of pesticides via breast feeding should be taken into consideration. Due to measurements from a 20 year monitoring programme for persistent organochlorine compounds show, that the uptake (95^{th} percentiles) of e.g. HCH may account for ~0,7 , that of HCB for 0,75 and of DDT for 3,8 µg/kg of bodyweight per day.

V.5. Needs for improvement knowledge on exposure in childhood

The the most critical point is that knowlegde on data needed for exposure assessment in children is poor. This very general statement can be applied for data to be taken as variables in models, scenarios and models and for studies that validate the models. In the approach to use models for exposure assessment is taken as a basic concept, the following consequences must be kept in mind.

1. Models are mathematical expressions of scenarios. The most important prerequisition for modeling is therefore to characetrise the scenario as realistic as possible. There are lots of ideas on scenarios, either for single or for continous exposures.

2. Exposure can be measured. This means that either the total exposure (given as µg/m³) can be measured as a concentration reflecting external exposure, or as a process e.g. migration or ventilation, or as an input variable of a model.

Figure 1: Relationship of measurements and modeling of exposure and role of data.

The relationship between modeling and measurement of exposure can be understood as a circle: Models are needed because measurements cannot be performed for any case of exposure. Hovewer, only measurements can really quantitate the exposure. What is the interface between both? The answer is, data. An appropriate use of sufficient data would lead to adequate modeling of exposure and to its validation via selected measurements.

The key to improve exposure assessment is therefore to compile the data needed for modeling the exposure and to balance the values by measurements which must be performed hand in hand. For children, we have lots of data gaps that uncertain the exposure assessment. Most of these uncertainties have been figured out in the contributions to the workshop.

The most important aim of further work is therefore to (i) improve the database and (ii) validate models. This has been pointed out under the different subchapters of this report. Insufficient data bases are drawing through all the conclusions of the four working groups.

This means that for all of the parameters that are used for exposure assessment more certainty is needed. This applies for data which are characteristic for the exposed persons such as anthropometrics, behaviour, use characteristics, toxicokinetics, but also for those data that are independent of the person such as migrations, sinks and ventilation and the subsequent risk characterisation.

In the context of uncertainty it should be dicussed whether the variability of data can be included. This would mean that the distributions of unput variables have to be described in a proper statistical manner and that both - uncertainty and variability - are discriminated as far as possible. This means that distribution based (probabilistic) approaches should be evaluated for exposure assessments. Epidemiologic studies can improve data to describe age dependent changes in childhood.

Dedicated surveillance systems are needed to monitor children's exposure accidents and their health consequences.

V.6. Conclusion

Are children more sensitive than adults? When answering this question it should be considered that children are representing a population of their own. According to age, there are specific characteristics of scenarios, pathways of exposure and behaviour to be considered, together with the developmental aspects that must be also be taken into account.

Children are indeed a vulnerable population, but the effects are not steady during the whole childhood, changing qualitatively and quantitatively in relation to organ development. On the other hand, the capacity for elimination of substances changes, leading to decreases and increases of toxicity depending to the age. For exposure assessments, these specific characteristics of children's exposure should be considered as pointed out in this report.

VI. Autor's index

VII. Subjects index

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IX. Workshop Programme

Federal Institute for Health Protection of Consumers and Veterinary Medicine	bgvv

Workshop "Exposure of Children to Pesticides"

27th - 29th September, 2001, Berlin

Under the auspices of the "Action Programme Environment and Health" (the German National Environmental Health Action Plan supported by the German Federal Ministries for Health and the Environment, Nature Conservation and Nuclear Safety, the BgVV will organise a workshop "Exposure of Children to Pesticides". The workshop will address special problems of exposure assessment for children. Scenarios and approaches for exposure assessment will be discussed on the basis of exposures to pesticides which covers an important items of the " Forum *Children's, Environment and Health"* to be held in Munich on November 23rd and 24th.

venue:

Federal Institute for Health Protection of Consumers and Veterinary Medicine; Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, BgVV)

meeting place:

27. 9.2001: Umweltbundesamt, Corrensplatz 1, 14195 Berlin

28./29. 9. 2001: Harnack-Haus, Tagungsstätte der Max-Planck-Gesellschaft zur Förderung der Wissenschaften

Ihnestraße 16-20, 14195 Berlin

The workshop will be held with ca. 30 invited experts working on health and exposure assessment, risk assessment for pesticides and statistics.

The main objective of the workshop is to prepare a proposal for an approach of exposure assessment for children. In this context, the residential exposure to pesticides will be taken as an example The workshop will elaborate minimal requirements which are needed to perform an adequate assessment. This includes the characterisation of the use of substances and products, how they are released and transferred to the site of exposure, e.g. by residential contact after use by professionals or consumers, via contamination of indoor air, dust, soil, and food.

To address the question of children as a vulnerable population, toxicogenetics and toxicokinetics will be discussed, as well as children's special behaviour, e.g. mouthing, and health effects that can be observed.

Because measurement data are seldomly available to perform residential exposure assessments, models need to be developed. Data to be fed into those models need validation.

The consideration of variability and uncertainty of the data, models, and the respective results has obtained an increased importance. The impact of statistical methodology and the advantages and limits of probabilistic a ssessments will be addressed.

The workshop will be divided into three parts on three days:

Day one: Lectures giving overviews of the main items will be held to the plenum. This first day is also open for other interested persons, registration will be required.

Day two: Closed working groups will be formed to work out recommendations.

Day three: Presentation and discussion of the papers in the plenum.

After the workshop, the papers will be reviewed and finalised by e-mail under the coordination of the chairs and rapporteurs of the working groups.

Agenda

Thursday, 27th September

On the first day, invited lectures are planned to cover the following items (9°° 18°°):

Are children more vulnerable than adults?

- Influence of age on factors that limit the internal exposure
  (W. Snodgrass, Houston, TX)
- Impact of pharmacogenetics for toxicity of xenobiotics in children
  (M. Schwab, Stuttgart, D)
- Behaviour patterns as a specific factor limiting exposure of children
  (B. Steenbekkers, Bilthoven, NL)

Characerisation of pesticide exposure to children

- Heavy metals, pentachlorphenol, pyrethroids, and allergens in house dust from children's dwellings
  (U. Frank, Leipzig, D)
- Pathways of pesticide exposures for children
  (K. van der Jagt, Zeist, NL)
- An overview and characterization of the use of pesticides in German households
  (J. Herrmann, Berlin, D)
- The EPA childrens pesticides exposure measurement program
  (L. Sheldon, Research Triangle Park, NC)

Health effects in children from pesticide exposures

- The WHO-survey for the identification of health hazards to pesticide exposures
  (N. Besbelli, Geneva, CH)
- Biomonitoring for the assessment of exposure to some pyrethroid pesticides in Frankfurt
  (U. Heudorf, Frankfurt, D)
- Health effects from exposure to pesticides in Germany
  (H. Desel, Göttingen, D)
- A Review of the Effects ofLow-level Exposure to OP Pesticides in Children.
  (J. Hughes and A. Capleton, Leicester, UK)

Estimation of exposure by modelling and/or measuring

- What is needed for modelling exposure to pesticides?
  (H. Ozkaynak, Research Triangle Park, NC)
- Requirements for models used for exposure assessment to pesticides.
  (L. Rosenheck, Greensboro, NC)
- Deterministic versus probabilistic estimation of exposure?
  (O. Mosbach-Schulz, Bremen, D)
- Uncertainty and variability of exposure data
  (O. Mekel, Bielefeld, D)

In addition to lectures, studies related to the workshop objectives will be presented as posters.

1. Exposure to kreosote to children from wood-impregnation on playing grounds
   (A. Boehncke, Hannover, D)
2. Homes with wool carpets, treated with permethrin - Exposure of adults and children
   (E. Berger-Preiß, Hannover, D)
3. German Environmental Survey 1990/92 (GerES II) and 1998 (GerES III): PCP in urine of the German population - spatial and temporal differences
   (C. Schulz, Berlin, D)
4. German Environmental Survey 1998 (GerES III): Biocides in house dust
   (K. Becker, Berlin, D)
5. Biocide emissions from indoor wall paints
   (Horn, Berlin D).
6. Areas of High Agricultural Pesticide Use in California:
   How Many Children Live There?
   (M. Harnly, Oakland, CA)
7. Dokumentation of pesticide use in the European Union
   (L. Neumeister, Hamburg, D
8. Models of exposure assessment of undesirable substances in foods - adults and children
   (B. Schmidt-Faber, Berlin,D).
9. Evaluation of symptoms from acute and chronic exposures of organophosphates and pyrethroids
   (A. Hahn, Berlin)
10. Pesticides in mother's milk
    (B. Vieth, Berlin)

Friday, 28th September

9^{00} - 18^{00} working groups

Working group 1:

Children as a vulnerable group?

Topics to be addressed: Toxicokinetics, toxicogenetics, health effects of pesticide exposures in children

Chairman: **W. R. Snodgrass, Chairperson**

Rapporteur: **F. Bois, G. Charnley**

Working group 2:

Modelling exposure of children to pesticides.

Topics to be addressed: Scenarios and models of exposure estimation, needs for data, uncertainty and variability.

Chairman: **M. Schümann**

Rapporteur: **J. van Engelen, O.Mekel**

Working group 3

Residential uses of pesticides

Topics to be addressed: Identification and characterisation of main pesticide uses in households, direct and indirect uses

Chairman: **C. Lunchick**

Rapporteur: **L. Neumeister, K. van der Jagt**

Working group 4

Behaviour of children as a factor determining exposure,

Topics to be addressed: Behaviour of children that leads to typical exposures, children's time budgets

Chairman: **S. Olin**

Rapporteur: **B. Steenbekkers, N. Freeman**

Saturday, 29th September

Plenum discussion

9°°	**Report of the 1st working group**	
9^{30}	**Discussion and further resumee**	
10^{15}	**Coffee break**	
10^{45}	**Report of the 2nd working group**	
11^{15}	**Discussion and further resumee**	
12^{00}	**Lunch break**	
13^{00}	**Report of 3rd working group**	
13^{30}	**Discussion and further resumee**	
14^{15}	**Report of 4th working group**	
14^{45}	**Discussion and further resumee**	
15^{30}	**Closing ceremony**	
16^{00}	**End of the meeting**	