ATTACHMENT 2

Center for Regulatory Effectiveness

March 2003

EXCERPTS FROM ADDITIONAL[1] INTERNATIONAL CODES/GUIDANCE/OPINIONS ON HUMAN VOLUNTEER STUDIES AND THEIR USE IN RISK ASSESSMENT[2]

Notes:

- All of the material below that is block indented is quotation.
- The materials are arranged in reverse chronological order – *i.e.*, with the most recent material first.

1. European Commission Scientific Committee on Plants[3], 2002

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE DOCUMENT ON THE SETTING OF ACCEPTABLE OPERATOR EXPOSURE LEVELS (AOEL) (Doc. SANCO/7531/VI/95-rev6 dated 10 September 2001)

(Opinion adopted by the Scientific Committee on Plants on 23 October 2002)

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[1] "Additional" here means in addition to the Nuremberg Code (1947) and the Declaration of Helsinki (initially published in 1964; last revised in 2000).

[2] The focus here is on codes, etc. which address controlled human exposures to substances without a therapeutic purpose. There are several codes which focus on testing of medicinal products; however, even those codes, etc. either do not require an expectation or possibility of therapeutic benefit to subjects, or are silent on the issue involved in this project (NAS Project STLP-Q-02-02-A). For example, the recently published International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), 2002, includes within its definition of covered research "studies of a physiological, biochemical or pathological process, or of the response to a specific intervention – whether physical, chemical or psychological – in healthy subjects or patients . . . . [Such] research may be concerned with the social environment, manipulating environmental factors in a way that could affect incidentally-exposed individuals. It is defined in broad terms in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for health-related purposes." And see Directive 2001/20/EC of the European Parliament and of the Council, 4 April 2001, concerning good clinical practice in the conduct of clinical trials on medicinal products for human use.

[3] The mandate of the SCP encompasses pesticide use.

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The SCP is of the opinion that human data are most useful because they provide reassurance on the extrapolation process; however, apart from ethical issues, it is stressed that human data should be used in the context of the entire toxicological profile of the PPP [pesticide plant product] under consideration. This also applies to human data obtained from monitoring operators and re-entry workers.

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2.9 Human data are most useful because they provide reassurance on the extrapolation process. However, the SCP noted that, apart from ethical issues, studies conducted in humans may have limitations (e.g. reduced number of subjects, the use of only one sex, the possibility of studying only selected end-points). The SCP stresses that human data should be used in the context of the entire toxicological profile of the PPP under consideration (see also the opinion on the draft guidance document on Acute Reference Dose [see below]). This also applies to human data obtained from monitoring operators and re-entry workers.

2. JMPR report: "Pesticide Residues in Food – 2002"

Report of the Joint Meeting of the
FAO Panel of Experts on Pesticide Residues
in Food and the Environment
and the WHO Core Assessment Group on Pesticide Residues
Rome, Italy
19- 25 September 2002

[Note: EPA has a number of personnel on the JMPR, including several from its Office of Pesticide Programs.]

Use of human data

Human data on a pesticide, whether from volunteer studies or from other investigations of human exposures in the workplace or environment, can be extremely valuable in placing the animal data in context and, when available, should always be evaluated even when they are not used to derive an acute RfD. However, when performing a risk assessment on a pesticide, the entire database should be considered and the most appropriate studies and safety factors used to derive reference values.

Evaluators should consider the following issues in determining whether to use a volunteer study in the derivation of an acute RfD:

The initial consideration should be scientific merit. A poorly designed or

conducted study in humans (as with experimental animals) should not be used for establishing an acute RfD.

The acceptable group size will depend on factors such as inter-individual variation in response and the level of change considered not to be adverse. The studies should be assessed with particular consideration of their power to detect critical effects.

The IPCS Guidance for the use of chemical-specific adjustment factors proposed a minimum group size of 5^6.[4] Studies using small group sizes might be useable, e.g. by combining results from two or more dose levels or applying an increased safety factor.

The critical end-points identified in animal studies should be investigated appropriately in human studies.

If only one sex or a particular age group has been used, the general applicability of the results should be ascertained, if possible, using data from studies in animals.

As recommended by the 1998 JMPR, recent studies in humans should include clear statements that they were performed in accordance with internationally accepted ethical standards. For older studies, ethical considerations should take into account both current standards and the standards pertaining at the time the study was performed.

Studies that have not been performed in accordance with ethical principles but are scientifically valid should be used only if the findings indicate that acceptable human exposure is lower than the level that would be determined without the use of such a study.

3. European Commission Scientific Committee on Plants, 2002

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE DRAFT GUIDANCE DOCUMENT FOR THE SETTING OF AN ACUTE REFERENCE DOSE (ARFD)

(Opinion adopted by the Scientific Committee on Plants, 18 July 2002)

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[4] See section 5. The references to minimum number of human subjects are in sections 3.1.3 4) and 3.2.3 3) of the Guidance document.

Human data are most useful because they provide reassurance on the extrapolation process. However, the Committee noted that, apart from ethical issues, studies conducted in humans may have limitations (e.g. reduced number of subjects, the use of only one sex, the possibility of studying only selected end-points). The Committee stresses that human data should be used in the context of the entire toxicological profile of the PPP under consideration.

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7. Use of human data (re 2.10, 2.33, 2.34, 2.35)

This issue refers mainly, although not exclusively, to single or short-term exposures. Human data are most useful because they provide reassurance on the extrapolation process. However, the Committee noted that, apart from ethical issues, studies conducted in humans may have limitations (e.g. reduced number of subjects, the use of only one sex, the possibility of studying only selected end-points). The Committee stresses that human data should be used in the context of the entire toxicological profile of the PPP under consideration.

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Re 2.10 (and Re 2.35): See General comment 8 [sic – apparently 7, above, since there is no 8]. Last sentence of 2.10 should be removed (it is unclear how "the ethical status of human studies" could be "established"); the Committee also believes that all available human studies always deserve consideration.

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Re 5.3: Ethical considerations and usefulness of human data are independent concepts. This sentence should be better formulated.

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[Initial statement above – "Human data are most useful . . . . – repeated.]

4. <u>International Programme on Chemical Safety (WHO/IPCS/IOMS), 2001</u>

Environmental Health Criteria 223

ENVIRONMENTAL HEALTH CRITERIA FOR NEUROTOXICITY RISK ASSESSMENT FOR HUMAN HEALTH: PRINCIPLES AND APPROACHES

[Note: These recommendations were prepared by an expert committee in which EPA and NIEHS participated.]

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

World Health Organization Geneva, 2001

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4.3.3 Human experimental exposure studies

In addition to epidemiological studies, well conducted experimental exposure studies in humans are also an important source of information for neurotoxicity risk assessment. Human laboratory experiments involve short-duration exposures (i.e., 2-6 h) for one or several consecutive days by the inhalatory route using either a mask or a controlled environmental chamber. Because many organic solvents are regulated on the basis of acute effects (Kulig, 1996), most studies have been conducted to evaluate the effects of these compounds, often in conjunction with toxicokinetic studies (Dick, 1995). In a typical laboratory study, solvent concentrations in blood are measured before, during and following exposure, and effects on the nervous system are assessed using symptom ratings, behavioural performance tests or electrophysiological methods. Most studies have been conducted in subjects under non-workload (i.e., sedentary) conditions. However, several studies have attempted to introduce "peak exposures" by either incorporating a workload condition (i.e., physical exercise), which has the result of increasing internal blood levels of exposure, or introducing periods of fluctuating high exposure peaks. Table 7 lists some of the solvents that have been studied in human laboratory studies alone or in combination with other chemicals and drugs.

Table 7. Solvents and combinations studied in human laboratory experiments[a]

acetone / acetone and methyl ethyl ketone (MEK) / carbon tetrachloride / Fluorocarbon 113 / MEK / methyl chloride (chloromethane) / methyl chloride and ethanol / methyl	perchloroethylene (PER) (tetrachloroethylene) / PER and ethanol / PER and diazepam / styrene / toluene / toluene and ethanol / toluene and MEK / toluene and xylene /

chloride and diazepam / methyl chloroform (1,1,1-trichloroethane) / methylene chloride (dichloromethane) / methyl isobutyl ketone (MIBK) / MIBK and MEK / MIBK and toluene / propylene glycol dinitrate (jet fuel) /

trichloroethylene / trichloroethylene and ethanol / trichloroethylene and meprobamate / trichloroethylene and thonzylamine / vinyl chloride / white spirit / xylene / xylene and ethanol / xylene and methyl chloroform

[a] From Dick (1995). [Dick RB (1995) Neurobehavioral assessment of occupationally relevant solvents and chemicals in humans. In: Chang LW & Dyer RS ed. Handbook of neurotoxicology. New York, Marcel Dekker, pp 217-322.]

From a methodological standpoint, human laboratory studies can be divided into two categories: between-subject and within-subject designs. In the former, the performance of exposed volunteers is compared with that of non-exposed participants. In the latter, performance is measured in the same individuals under exposure and non-exposure conditions. Within-subject designs have the advantages of requiring fewer participants and of eliminating individual differences as a source of variability. A disadvantage of the within-subject design is that certain tests, including neurobehavioural tests, must be administered more than once. Since practice on some neurobehavioural tests often leads to improved performance, which may confound the effect of the chemical/drug, there should be a sufficient number of test sessions in the pre-exposure phase of the study to allow performance on all tests to achieve a relatively stable baseline level.

Participants in laboratory exposure studies may be recruited from populations of persons already exposed to the chemical (e.g., solvent workers) or from chemically naive populations. Chemically naive volunteers are often younger, healthier and better educated than those exposed in the workplace and therefore may be less vulnerable to neurotoxicants.

Compared with workplace and environmental exposures, laboratory exposure conditions can be controlled more precisely, but exposure periods are much shorter, and ethical considerations limit the dose that can be given. In addition, double-blind studies have been shown to provide some control for the observer bias that may occur in single-blind studies. More credence should be given to those studies in which both observer bias and subject bias are carefully controlled (Benignus, 1993).

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6.2.3 Special issues

6.2.3.1 Animal-to-human extrapolation

The use of animal data to identify hazards for humans is not without controversy. Relative sensitivity across species as well as between sexes is a constant concern. Overly conservative risk assessments, based on the assumption that humans are always more

sensitive than a tested animal species, can result in poor risk management decisions. Conversely, an assumption of equivalent sensitivity in a case where humans actually are more sensitive to a given agent can result in underregulation, which might have a negative impact on human health. Interspecies comparisons of kinetics and biotransformation pathways are an important component of interspecies extrapolation.

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6.2.1 Human studies

Information obtained through the evaluation of human data often can provide direct identification of neurotoxic hazards. Well documented observational, clinical and epidemiological studies have the clear advantage over studies in animals in providing the most relevant information on human health effects (ECETOC, 1992; US EPA, 1998a). With the exclusion of therapeutic agents, information on effects in humans consists primarily of case reports of accidental exposures, occupational exposures, epidemiological studies and ethically conducted human volunteer studies (see chapter 4).

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REFERENCES

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US EPA (1998a) Guidelines for neurotoxicity risk assessment. United States Environmental Protection Agency. Fed Regist, **63**: 26926-26951.

5. International Programme on Chemical Safety (WHO/IPCS/IOMS), 2001

Guidance Document for the Use of Data in Development of Chemical Specific Adjustment Factors (CSAFs) for Interspecies Differences and Human Variability in Dose/Concentration-Response Assessment

[Note: Personnel from the U.S. EPA assisted in the preparation of this guidance.]

1.2 Objectives

The principal objectives of the development of this guidance document are 1) to increase common understanding and to encourage the incorporation of relevant quantitative data in a context consistent with traditional approaches to development of measures of dose/concentration-response, and 2) to more fully delineate appropriate avenues of research to enable more predictive estimates of risk. With respect to the latter objective,

this approach necessarily requires ethically derived human data from either *in vivo* or *in vitro* studies in order to inform the selection of appropriate adjustment factors for interspecies differences or human variability. . . .

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2.3.1 *Traditional approach to consideration of measures of dose/concentration-response for threshold toxicants*

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. . . When data are available from direct experimentation in groups of human volunteers, the NOAEL has traditionally been divided by an uncertainty factor of 10 to allow for human variability. . . .

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3.2 **Data for the development of a chemical-specific adjustment factor for interspecies differences in toxicodynamics (AD_{AF}) . . . .**

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. . . If there are adequate *in vivo* data in humans, the measure of dose-response (i.e., effect level or BMD [benchmark dose] would generally be used directly and there would be no need to extrapolate from *in vivo* animal data using an interspecies adjustment factor.

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[And see case studies A and B in Appendix I, which assume use of human volunteer data.]

6. <u>International Programme on Chemical Safety (WHO/IPCS/IOMS), 1999</u>

Environmental Health Criteria 210

PRINCIPLES FOR THE ASSESSMENT OF RISKS TO HUMAN HEALTH FROM EXPOSURE TO CHEMICALS

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization. Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

World Health Organization Geneva, 1999

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3.2 Human data

Well-documented observational and clinical epidemiological studies have the clear advantage over studies in animals in providing the most relevant information on health effects in the species of interest, thus avoiding extrapolation from animals to humans.

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Ethical experimental studies in human volunteers offer the advantage of being better able to control for confounding factors. The assignment of study subjects to exposure groups is made by the investigator, who also controls the quality and quantity. Although such investigations are generally reliable for the establishment of both causality and exposure-response relationships, they are most often restricted for ethical reasons to the examination of mild, temporary effects (e.g., neurobehavioural or biochemical changes) of short-term exposures in a limited number of subjects. They have contributed considerably, particularly to our understanding of kinetics and to the development of air quality guidelines and standards for traditional pollutants.

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4.3.2 Uncertainty factors

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d) Inter-species extrapolation

The inter-species uncertainty factor is not necessary if the NOAEL or risk assessment is based on human data. Where an assessment is based on data in animals, however, and in situations where there are appropriate compound-specific toxicokinetic and/or toxicodynamic data, the relevant default uncertainty factor for inter-species variation would be replaced by the data-derived factor (Renwick, 1993b). Data on physiologically based pharmacokinetic (PBPK) modelling should be included wherever possible; however, such information is available currently for only a small number of substances.

7. International Programme on Chemical Safety (WHO/IPCS/IOMS), 1994

Environmental Health Criteria 170

**ASSESSING HUMAN HEALTH RISKS OF CHEMICALS:
DERIVATION OF GUIDANCE VALUES FOR
HEALTH-BASED EXPOSURE LIMITS**

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

First draft prepared at the National Institute of Health Sciences, Tokyo, Japan, and the Institute of Terrestrial Ecology, Monk's Wood, United Kingdom Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

World Health Organization Geneva, 1994

[Note: The WHO Task Group that developed this guidance included U.S. representatives from ATSDR and EPA. Development of the Guidance was also supported by a grant from NIH.]

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3.1 Approaches to risk assessment

. . . . Wherever possible, appropriate human data should be used as the basis for the risk assessment.

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4.4 Interspecies extrapolation

In situations where appropriate toxicokinetic and/or toxicodynamic data exist for a particular compound, then the relevant uncertainty factor in Fig. 3 should be replaced by the data-derived factor. Data on PBPK and/or data on target organ exposure should be included when they are available. Subdivision of the 10-fold uncertainty factor has been used in the development of a reference concentration for 1,2-epoxybutane (US EPA, 1993). Chemicals for which the approach described here has been applied include saccharin (Renwick, 1993b), erythrosine (Poulsen, 1993), butylated hydroxyanisole (BHA) (Wurtzen, 1993) and diethylhexyl phthalate (DEHP) (Morgenroth, 1993).

If a data-derived factor is introduced then the commonly used 10-fold factor would be replaced by the product of that data-derived factor and the remaining default factor. For some classes of compounds a data-derived factor for one member of the class may be applicable to all members, thereby producing a group-based data-derived factor (see Calabrese, 1992). The interspecies uncertainty factor is not necessary if the NOAEL or LOAEL is based on human data.

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8. International Programme on Chemical Safety (WHO/IPCS/IOMS) in cooperation with the Joint FAO/WHO Expert Committee on Food Additives (JECFA), 1987

Environmental Health Criteria 70

PRINCIPLES FOR THE SAFETY ASSESSMENT OF FOOD ADDITIVES AND CONTAMINANTS IN FOOD

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5.4. Use of Human Studies in Safety Evaluation

Human studies are not normally included in the data packages that JECFA reviews in its evaluation of new food additives. However, the Committee recognizes the value of human data, has sometimes requested such data, and has always used it in its evaluations when available. Data from controlled human exposure studies are useful in confirming the safety indicated by animal studies after the establishment of ADIs. Such data are also useful in subsequent periodic reviews, and might facilitate a re-evaluation of the safety factors that are applied in calculating ADIs.

Investigation in human subjects was addressed by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (2, pp. 9-10). The Group felt that

> "prediction and prevention of possible toxic hazards to the community that might arise from the introduction of a chemical into the environment can be made more certain if information from meaningful studies in human subjects is available." Three particular aspects of toxicology were identified in this connection, "the choice of the most appropriate animal species for. . . the prediction of human responses; secondly, the investigation of a reversible specific effect observed in the most sensitive animal species to determine whether it represents a significant hazard to man; thirdly, the study of effects specific to man."

The Group pointed to:

> "the need, at a relatively early stage, to obtain information on the absorption, distribution, metabolism, and elimination of the chemical in human subjects, since this makes it possible to compare this information

with that obtained in various animal species and to choose the species that are most likely to have a high predictive value for human responses."

This need has been reiterated by subsequent meetings of JECFA (27, p. 23; 16, p. 31; 32, p. 13) and in WHO Environmental Health Criteria 6 (76). However, the WHO Scientific Group acknowledged that "it is necessary to have adequate short-term toxicological information in several species before even low doses of a new chemical are administered to human subjects" (2, p. 9).

In relation to ascertaining whether the safety margin predicted from animal data is valid, the WHO Scientific Group decided that it might be helpful to administer a chemical to human volunteers, but emphasized the conditions that should be fulfilled with regard to such a study (2, p. 10). *Inter alia,* these conditions include:

(a) The effect or effects studied should be reversible.

(b) The dose levels used should be based on full information of the toxicological properties of the substance in animals.

(c) The investigation should be terminated immediately the effect has been unequivocally demonstrated.

With regard to effects specific to man, the WHO Scientific Group (2, p. 10) considered it unacceptable to study such effects by means of volunteers (in an analogous manner to clinical trials with drugs) but thought that toxicological studies could be made on those who are occupationally exposed to the chemical or in patients suffering from accidental poisoning. A need was identified for "more critical epidemiological and toxicological investigations in such situations." Such studies could be of particular value in relation to hypersensitivity or other idiosyncratic reactions since no suitable animal model has yet been developed. In relation to hypersensitivity, the seventeenth and eighteenth meetings of JECFA (16; 17, p. 10) stated that "no approval would be given for the use of a substance causing serious or widespread hypersensitivity reactions". However, such information can be derived only from studies on human beings.

The WHO Scientific Group has raised an apparent contradiction in its different recommendations with regard to confirming animal studies and investigating effects specific to man. As stated above, the Group recommended that controlled human studies be performed to confirm animal studies, but that it is inappropriate to study effects specific to man by the use of human volunteers. This is all the more perplexing, because controlled human studies, despite their limitations, are the only means available, at present, for studying effects in man that are not observed in animals. JECFA may wish to reconsider the question of using human volunteers to identify specific responses, which would be done

only after the usual battery of toxicological investigations had been completed. The words of Paget (77) are cogent in this regard:

> "The question is not whether or not human subjects should be used in toxicity experiments but rather whether such chemicals, deemed from animal toxicity studies to be relatively safe, should be released first to controlled, carefully monitored groups of human subjects, instead of being released indiscriminately to large populations with no monitoring and with little or no opportunity to observe adverse effects."

The ethical problems associated with toxicological studies on human beings have been reviewed succinctly in WHO Environmental Health Criteria No. 6 (76, pp. 41-42).

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5.5.2. Use of the safety factor

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5. If reasons exist for setting a lower safety factor

If toxicity and dose-response effects in human beings are known, such data should take precedence over extrapolation from animal studies; . . .

9. International Programme on Chemical Safety (WHO/IPCS/IOMS), 1978

Environmental Health Criteria 6

PRINCIPLES AND METHODS FOR EVALUATING THE TOXICITY OF CHEMICALS, PART I

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization. Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization World Health Organization Geneva, 1978

1.4 Human Data

1.4.1 Ethical considerations

In research involving human subjects, a number of elements, such as the assessment of risk, potential benefit, and quality of consent, have to be evaluated to ascertain whether ethical considerations are satisfied. The essential provisions for protecting human subjects in experimentation and research have been expounded by many international and national organizations. Key factors include the right to informed consent and freedom from coercion. The international instruments in dealing with this matter are the Declaration of Helsinki (as revised in Tokyo in 1975) and Article 7 of the International Covenant on Civil and Political Rights, adopted by the United Nations General Assembly, December 1966. Article 7 provides that "no-one shall be subjected without his free consent to medical or scientific experimentation" (Cranston, 1973; WHO, 1976b). Some countries possess specific codes of ethics relating to human experimentation, and special problems of experimentation that involve the use of fetuses, children, the mentally ill, and prisoners require special consideration.

It is essential that human experimentation should only be undertaken when there is adequate evidence from animal and other studies that both the chemical and the circumstances of administration are safe. Every experiment with human volunteers should be subject to prior review and approval by a local ethical committee in order to ensure that the intended study complies with the ethical principles embodied in the Declaration of Helsinki and with other requirements of national and local bodies.

Ideal conditions of truly informed consent may not always be achieved in practice, consequently the burden of responsibility rests mainly with the investigator and, to a lesser extent, with the peer review body. Because of these difficulties, the guidelines and procedures for the protection of human subjects should be constantly reviewed and updated (WHO, 1976b).

In any case, collection of data from human subjects must be accomplished with due respect for human rights and dignity. The use of ethics committees with broad representation to review and approve all such experimentation is recommended to protect the rights of human subjects and to ensure responsible investigation.

1.4.2 Need for human investigations

Although there is general repugnance at the idea of using human subjects to assess the safety of environmental chemicals, the question is not whether or not human subjects should be used in toxicity experiments but rather whether such chemicals, deemed from animal toxicity studies to be relatively safe, should be released first to controlled, carefully monitored groups of human subjects, instead of being released indiscriminately to large populations with no monitoring and with little or no opportunity to observe adverse effects (Paget, 1970).

The prediction and prevention of possible toxic hazards that may arise from the

introduction of chemicals into the environment can be made more valid if data from studies of the chemical in human subjects are available. Three particular aspects of human toxicology have need of such information, namely: (a) the selection, through comparative consideration of metabolism, of the most appropriate animal species for studies to predict the human response; (b) investigation of a specific, reversible effect of the compound in the most sensitive animal species, to determine whether there is a correlation with a similar effect in man; and (c) study of effects specific to man.

Certain types of information about the effects of chemicals can only be obtained by direct observations on man. Often, carefully controlled experiments can provide significant information at doses well below those anticipated to be "safe"; measurement of subtle changes of reaction time, behavioural functions, and sensory responses may be examples. In other cases, useful information may be obtained by careful studies on human cells or tissue maintained by culture techniques.

Human toxicological data include both the data obtained from epidemiological surveys of populations exposed to a toxic chemical under normal conditions of use, in cases of acute accidental poisoning and in occupational exposure, and the data from experiments in volunteers. Although an experiment is defined as observations under controlled conditions of exposure, there is, at times, only a grey area that distinguishes an experiment with human subjects from observations on human subjects under natural conditions. For example, some segments of human populations are at higher risk and should be particularly closely monitored, e.g., those exposed to chemicals at work or those receiving continuous treatment with medicines. The periodic clinical evaluation of workers is normally the responsibility of the employer and careful records of these examinations coupled with measurement of exposure conditions often exist. If accidental excessive exposure of an individual or a population should occur, it is both ethical and pertinent to learn as much as possible, recognizing always the right of the patient. Because of the wide individual variation in the toxicity of chemicals to man, the final evaluation should be based on information obtained from as widely varied a human population as is compatible with the various ethical principles involved.