BIOMEDICAL AND ENVIRONMENTAL SCIENCES 8, 1-13 (1995)

Safety/Risk Assessment of Chemicals Compared for Different Expert Groups[1]

MICHAEL L. DOURSON* AND FRANK C. LU**,[2]

** Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Cincinnati, Ohio, USA;*
*** 7452 S.W. 143 Ave., Miami, FL 33183, USA*

Two sets of 65 risk/safety assessments are compared. These assessments, mostly for pesticide chemicals, were developed by the World Health Organization (WHO) and the U.S. Environmental Protection Agency (EPA) at different times, often with different toxicity data, and with slightly different methods. Despite these differences, 38 sets of assessments give values that are within a 3-fold range of each other; 18 of these 38 are essentially identical (when rounded to one digit of precision), although not always for the same reasons. An additional 20 sets give values that lie within a 30-fold range; 6 sets lie within a 300-fold range; and the bromomethane ADI and RfD are 700-fold apart. In addition, on average the EPA values are lower than the WHO numbers.

These comparisons are discussed in relationship to a developing world-wide consensus that the methods for evaluating the safety/risks from various chemicals should be more consistent and the resulting assessments should be more comparable. Moreover, we argue that an established assessment and associated information from one expert group should be routinely discussed in the ongoing evaluation of a chemical by another expert group. A procedure for effecting more consistency among such expert groups is proposed.

INTRODUCTION

Over the last three decades, the U.S. Food and Drug Administration (FDA), the World Health Organization (WHO), the U.S. Environmental Protection Agency (EPA) and other health organizations throughout the world developed methods to assess public health risk from chemical exposures. In 1961, WHO began annual meetings of experts to assess and reassess food additives, contaminants and pesticides and establish, where appropriate, ADIs (Acceptable Daily Intakes). The inception, evolution and application of this assessment procedure have been summarized (Lu, 1988) and critically reviewed (Lu and Sielken, 1991).

Since the 1970s, the EPA has been carrying out similar activities involving pesticides and other chemicals. The EPA procedure involves the selection of a No-Observed-Adverse-Effect Level (NOAEL) for the critical effect, and applying an

[1] Presented in part at the XIIth International Congress on Pharmacology, Montreal, Canada, July 24-29, 1994.

[2] Consulting toxicologist, Miami, Florida, USA; former Chief, Food Additives and Contaminants Unit, World Health Organization.

0895-3988/95
CN 11-2816
Copyright © 1995 by CAPM

uncertainty factor (UF) to obtain the RfD (Reference Dose). Details of this assessment procedure have been presented by Dourson and Stara (1983); and Barnes and Dourson (1988).

The procedures used by WHO and EPA, while essentially similar, differ in certain ways, hence there have been differences in the ADIs and RfDs. In a previous paper (Lu and Dourson, 1992), the guiding principles used by these two groups were examined in connection with 27 pesticides. It was noted that of the 13 pesticides that had both ADIs and RfDs, these two sets of values were similar in most cases. But with DDT, there was a 40-fold difference, and somewhat smaller differences between the values with a few other pesticides.

The purpose of this paper is to extend the work of Lu and Dourson (1992) and compare 65 pesticides that have both ADIs and RfDs. This comparison demonstrates the need for re-evaluation of several of them. More importantly, as new scientific advances occur, more opportunities exist for revising risk assessment methods. The pursuit of these revisions should perhaps be coordinated or unified worldwide. See for example a recent publication of the International Programme on Chemical Safety (IPCS) towards this effort of harmonization within its development of environmental criteria (IPCS, 1994). We also suggest a simple procedure for effecting more consistency among expert groups, and motivating international efforts towards harmonization of the underlying risk assessment methods.

METHODS

Terminology

Below are some common definitions used in noncancer risk assessment. These definitions are for illustration only. Other terms are used in different organizations and countries.

Acceptable Daily Intake: The daily intake of a chemical which, during a lifetime, appears to be without appreciable risk on the basis of all the known information at the time.

Adverse Effect: A biochemical change, functional impairment, or pathological lesion which impairs performance and reduces the ability of the organism to respond to additional challenge.

Critical Effect: A chemical often elicits more than one toxic effect, even in one species, or in tests of the same or different durations. The critical effect(s) is the first adverse effect(s) or its known precursor(s) that occurs as dose rate increases. The critical effect(s) may change among toxicity studies of different durations, may be influenced by toxicity in other organs, and may differ depending on the availability of data on the shape of the dose-response curve.

Lowest-Observed-Adverse-Effect-Level (LOAEL): The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

No-Observed-Adverse-Effect Level (NOAEL): An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; *some effects may be produced at this level, but they are not considered as adverse, nor precursors to*

specific adverse effects. In an experiment with several NOAELs, the regulatory focus is primarily on the NOAEL seen at the highest dose. This leads to the common usage of the term NOAEL to mean the highest exposure without adverse effect.

Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime.

Uncertainty Factor (UF)/Safety Factor (SF): One of several, generally 10-fold, factors used in operationally deriving an RfD or ADI from experimental data. Among other things Ufs are intended to account for (i) the variation in sensitivity among the members of the human population; (ii) the uncertainty in extrapolating animal data to the case of humans; (iii) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure; (iv) the uncertainty in using LOAEL data rather than NOAEL data; and (v) the inability of any single study to address adequately all possible adverse outcomes in man.

Sources of Information

The critical effects, NOAELs (no-observed adverse effect levels), safety factors (Sfs), and ADIs were taken from the relevant WHO Reports and Monographs. All pesticides that have been evaluated, along with the year of their evaluation and reevaluation, and ADIs are listed alphabetically in a recent WHO publication (WHO, 1994).

The Integrated Risk Information System (IRIS) is a computer data base developed and maintained by EPA of chronic noncancer and cancer health hazard information (e.g., RfDs) for over 500 substances (U.S. EPA, 1994). It is the EPA's primary source for the Agency's consensus risk information and is available to a wide range of users including EPA staff, state agencies and the general public.

The latest ADIs (WHO, 1994) and RfDs (U.S. EPA, 1994) were compared on the basis of mg of chemical per kg of body weight per day, and absolute values of the resulting ratios were determined. No attempt was made to convert or modify the ADI or RfD on the basis of differences in toxicity data, year of estimation, or underlying method.

RESULTS

Table 1 shows the summary information for EPA's RfDs and WHO's ADIs for 65 chemicals, mostly pesticides. This information was obtained from the most recent sources as specified in the methods. Differences exist in descriptions of critical effects, judgments of experimental doses, choices of uncertainty (EPA) or safety (WHO) factors, and year of evaluation. Absolute values of the ratios of ADI to RfD were determined as specified in methods. In most cases the resulting RfDs and ADIs differ only slightly; however, on occasion substantial differences exist.

Thirty-eight of 65 ratios fall within 3-fold of each other. Ratios in this range indicate that the corresponding risk assessment values are relatively close. In 18 cases, they are 1, indicating that the ADI and the RfD are essentially the same value, although not always for the same reasons.

However, an additional 20 ratios range between 3- and 30-fold apart. Six additional

TABLE 1

WHO ADIs and U.S. EPA RfDs and Their Bases[a]

Chemical/CASRN	Org.	Critical Effect	Experimental doses ($mg \cdot kg^{-1} \cdot day^{-1}$)	UF or SF	RfD or ADI ($mg \cdot kg^{-1} \cdot day^{-1}$)	Difference in ADI Versus RfD[b]	Latest year of evaluation by EPA or JMPR[c]	Confidence in RfD
Acephate	EPA	Inhibition of AChE[d]	LOAEL: 0.12	30	0.004	8	1989	High
30560-19-1	WHO	Inhibition AChE, human	NOAEL: 0.3	100	0.03		1990	-
Aldicarb 116-06-3	EPA	Inhibition of AChE & clinical signs, human	NOAEL: 0.01	10	0.001	3	1992	Medium
	WHO	Inhibition AChE, human	NOAEL: 0.025	10	0.003		1992	-
Aldrin	EPA	Liver toxicity	NOAEL: 0.025	1000	0.00003	3	1985	Medium
309-00-2	WHO	Liver changes	NOAEL: 0.025	250	0.0001		1977	-
Amitraz 33089-61-	EPA	Increased blood sugar & hypothermia, dog	NOAEL: 0.25	100	0.0025		1987	Medium
	WHO	CNS depression, dog	NOAEL: 0.25	100	0.003		1990	-
Benomyl 17804-35-2	EPA	Decrease pup weanling weights	NOAEL: 5	100	0.05	3	1986	High
	WHO	Liver damage, dog	NOAEL: 2.5	100	0.02		1983	-
Bentazone	EPA	Prostatitis, dogs	NOAEL: 2.5	1000	0.0025	40	1986	Low
25057-89-0	WHO	Renal effects	NOAEL: 10	100	0.1		1991	-
Bifenthrin Biphenthrin (EPA)	EPA	Tremors, dog	NOAEL: 1.5	100	0.015		1988	High
82657-04-3	WHO	CNS effects, tremors, dog	NOAEL: 1.5	100	0.02		1992	-
Bromomethane	EPA	Hyperplasia of forestomach	NOAEL: 1.4	1000	0.0014	700	1988	Medium
74-83-9	WHO	CNS depression, human	NOAEL: 10	10	1.0 as bromide ion		1966	

(to be continued on the next page)

(continued)

Captan 133-06-2	EPA	Decrease in pup litter weights	NOAEL: 12.5	100	0.13	1	1989	High
	WHO	Effects on reproduction	NOAEL: 12.5	100	0.1		1990	-
Carbaryl	EPA	Kidney & liver toxicity	NOAEL: 9.6	100	0.1	10	1985	Medium
63-25-2	WHO	Effects on reproduction	NOAEL: 10	1000	0.01		1973	-
Carbofuran	EPA	Inhibition of AChE, dog	NOAEL: 0.5	100	0.005	2	1987	High
1563-66-2	WHO	Inhibition of AChE	NOAEL: 1.0	100	0.01		1982	-
Carbosulfan	EPA	Decreased body weight	NOAEL: 1	100	0.01		1986	High
55285-14-8	WHO	Possible cataract, mouse	NOAEL: 1.3	100	0.01		1986	-
Chlordane	EPA	Liver hypertrophy	NOAEL: 0.055	1000	0.00006	8	1989	Low
57-74-9	WHO	Regional liver hypertrophy	NOAEL: 0.05	100	0.0005		1986	-
Chlorobenzilate 510-15-6	EPA	Decrease body weight, rabbit	NOAEL: 5	300	0.02		1989	Medium
	WHO	Testicular damage	NOAEL: 2.0	100	0.02		1980	-
Chlorothalonil 1897-45-6	EPA	Renal tubule epithelial vacuolation, dog	NOAEL: 1.5	100	0.015	2	1986	Medium
	WHO	Renal tubule epithelial vacuolation	NOAEL: 3.0	100	0.03		1992	
Chlorpyrifos 2921-88-2	EPA	Inhibition of AChE, human	NOAEL: 0.03	10	0.003	3	1986	Medium
	WHO	Inhibition of AChE, human	NOAEL: 0.1	10	0.01		1982	
Cyhalothrin 68085-85-8	EPA	Reduced body weight gain	NOAEL: 0.5	100	0.005	4	1987	High
	WHO	Testicular degeneration	NOAEL: 1.5	100	0.02		1984	-
Cypermethrin	EPA	GI trace disturbances, dog	NOAEL: 1	100	0.01	5	1989	High
52315-07-8	WHO	Lower body weight gain	NOAEL: 5.0	100	0.05		1981	-

(to be continued on the next page)

(continued)

Cyromazine 66215-27-8	EPA	Hematologic effects, dog	NOAEL: 0.75	100	0.0075	3	1986	High
	WHO	Body weight changes	NOAEL: 2.0	100	0.02		1990	-
2,4-D 94-75-7	EPA	Hematotogic, hepatic & renal toxicity	NOAEL: 1.0	100	0.01	30	1986	Medium
	WHO	Embryotoxic effects	NOAEL: 31	100	0.3		1975	-
DDT	EPA	Liver lesions	NOAEL: 0.05	100	0.0005		1985	Medium
50-29-3	WHO	No lesions; higher dose in human	NOAEL: 0.25	10	0.02		1984	-
Demeton-S-methyl 8065-48-3	EPA	Inhibition of AChE & optic nerve degeneration	LOAEL: 0.04	1000	0.00004	8	1986	Low
	WHO	Inhibition of AChE	NOAEL: 0.03	100	0.0003		1989	-
Dichlorvos	EPA	Inhibition of AChE, dog	NOAEL: 0.05	100	0.0005		1992	Medium
62-73-7	WHO	Inhibition of AChE, human	NOAEL: 0.033	10	0.004		1977	-
Dieldrin	EPA	Liver lesions	NOAEL: 0.005	100	0.00005	2	1987	Medium
60-57-1	WHO	Liver changes	NOAEL: 0.025	250	0.0001		1977	-
Diflubenzuron 35367-38-5	EPA	Methemoglobin and sulfhemoglobin formation, dog	NOAEL: 2	100	0.02		1986	High
	WHO	Liver and kidney changes	NOAEL: 2.0	100	0.02		1985	-
Dimethipin	EPA	Increased liver weight	NOAEL: 2	100	0.02		1986	High
55290-64-7	WHO	Decreased adrenal weight	NOAEL: 2.0	100	0.02		1988	
Dimethoate	EPA	Brain AChE inhibition	NOAEL: 0.05	300	0.0002		1988	Medium
60-51-5	WHO	Inhibition of AChE, human	NOAEL: 0.2	20	0.01		1987	-
Diphenylamine/DPA 122-39-4	EPA	Decreased body weight & increased liver and kidney weights, dog	NOAEL: 2.5	100	0.025		1986	Medium
	WHO	Liver effects, dog	NOAEL: 2.5	100	0.02		1984	-
Diquat 85-00-7	EPA	Minimal lens capacity and cataracts	NOAEL: 0.22	100	0.0022	4	1986	Medium
	WHO	As above	NOAEL: 0.75	100	0.008		1978	

(to be continued on the next page)

(continued)

Disulfoton	EPA	AChE inhibition, optic nerve degeneration	LOAEL: 0.04	1000	0.00004	8	1986	Medium
298-04-4	WHO	Inhibition of brain AChE, dog	NOAEL: 0.03	100	0.0003		1991	-
Dodine	EPA	Thyroid toxicity, dog	NOAEL: 1.25	300	0.004	3	1987	Low
2439-10-3	WHO	Reproduction effects, dog	NOAEL: 1.25	100	0.01		1976	-
Endrin	EPA	Mild histological lesions in liver, occasional convulsions	NOAEL: 0.025	100	0.0003	2	1988	Medium
	WHO	Developmental effects, dog	NOAEL: 0.025	100	0.0002		1970	-
Ethion	EPA	Inhibition of AChE, humans	NOAEL: 0.05	100	0.0005	4	1989	Medium
563-12-2	WHO	Inhibition of brain AChE	NOAEL: 0.021	100	0.002		1990	-
Ethylenethiourea/ETU	EPA	Thyroid hyperplasia	NOAEL: 0.25	3000	0.00008	30	1991	Medium
96-45-7	WHO	Thyroid tumors	NOAEL: 1.8	1000	0.002 temporary		1988	-
Fenamiphos	EPA	AChE inhibition, dogs	NOAEL: 0.025	100	0.00025	2	1986	High
22224-92-6	WHO	Organ weight changes	NOAEL: 0.075	150	0.0005		1987	-
Folpet	EPA	Decreased body weight, dog	NOAEL: 10	100	0.1	10	1987	High
133-07-3	WHO	Keratosis in GI tract	NOAEL: 10	1000	0.01		1990	Temporary
Glufosinate-ammonium	EPA	Increased kidney weight	NOAEL: 0.4	1000	0.0004	50	1987	Medium
77182-82-2	WHO	Increased kidney weight	NOAEL: 2.1	100	0.02		1991	-
Glyphosate	EPA	Renal tubular dilation in F_{3b}	NOAEL: 10	100	0.1	3	1986	High
1071-83-6	WHO	Renal tubular dilation in F_{3b}	NOAEL: 31	100	0.3		1986	
Heptachlor/Heptachlor Epoxide	EPA	Liver weight increased	NOAEL: 0.15	300	0.005	5	1987	Low
76-44-8	WHO	Liver changes, dog	NOAEL: 0.025	200	0.0001		1991	

(to be continued on the next page)

(continued)

Hydrogen Cyanide 74-90-8	EPA	Weight loss	NOAEL: 11.2	500	0.02	3	1985	Medium
	WHO				0.05		1965	-
Imazalil 35554-44-0	EPA	Decreased body weight, dog	NOAEL: 1.25	100	0.013	2	1986	Medium
	WHO	Increased liver weight, dog	NOAEL: 2.5	100	0.03		1991	-
Iprodione 36734-19-7	EPA	Increased RBC Heinz bodies, dog	NOAEL: 4.2	100	0.04	5	1987	High
	WHO	Decreased body weight gain, rabbit	NOAEL: 20	100	0.2		1992	
Lindane (gamma-hexachloro-cyclohexane)	EPA	Liver and kidney toxicity	NOAEL: 0.33	1000	0.0003	30	1986	Medium
58-89-9	WHO	Liver and kidney changes	NOAEL: 0.75	100	0.008		1989	-
Malathion 121-75-5	EPA	Inhibition of AChE, human	NOAEL: 0.23	10	0.02		1987	Medium
	WHO	Inhibition of AChE, human	NOAEL: 0.2	10	0.02		1966	-
Maleic Hydraxide	EPA	Renal dysfunction	LOAEL: 500	1000	0.5	10	1988	Medium
123-33-1	WHO	Proteinuria	NOAEL: 500	100	5		1984	-
Maneb 17427-38-2	EPA	Increased thyroid weight, monkey	NOAEL: 5	1000	0.005	10	1987	Low
	WHO	Thyroid effects	NOAEL: 12.5	250	0.05		1980	-
Metalaxyl 57837-19-1	EPA	Increased SAP & liver to brain weight, dog	NOAEL: 6.25	100	0.06	2	1986	High
	WHO	Increased liver and adrenal weight	NOAEL: 2.5	100	0.03		1982	
Methamidophos 10265-92-6	EPA	Inhibition of AChE, dog	LOAEL: 0.05	1000	0.00005	100	1987	Medium
	WHO	Inhibition of AChE, human	NOAEL: 0.06	10	0.006		1990	

(to be continued on the next page)

(continued)

Methidathion 950-37-8	EPA	Liver toxicity, dog	NOAEL: 0.1	100	0.001		1988	
	WHO	Liver changes, dog	NOAEL: 0.1	100	0.001		1992	
Methomyl 16752-77-5	EPA	Kidney and spleen pathology, dog	NOAEL: 2.5	100	0.025		1986	High
	WHO	Kidney and spleen lesions	NOAEL: 2.5	100	0.03		1989	
Methoxychlor 72-43-5	EPA	Excessive loss of litters, rabbit	NOAEL: 5.0	1000	0.005	20	1990	Low
	WHO	Liver changes	NOAEL: 10	100	0.1		1977	-
Methyl Parathion	EPA	Inhibition of AChE	NOAEL: 0.025	100	0.00025		1986	Medium
298-00-0	WHO	Inhibition of AChE, human	NOAEL: 0.3	15	0.02	80	1984	-
Oxamyl 23135-22-0	EPA	Decreased body weight gain & food consumption	NOAEL: 2.5	100	0.025		1986	Medium
	WHO	Body weight changes	NOAEL: 2.5	100	0.03		1985	-
Paraquat 1910-42-5	EPA	Chronic pneumonitis, dog	NOAEL: 0.45	100	0.0045		1986	High
	WHO	Proliferative lung lesion	NOAEL: 1.6	400	0.004		1986	
Permethrin 52645-53-1	EPA	Increased liver weight	NOAEL: 5	100	0.05		1986	High
	WHO	Increased liver weight	NOAEL: 5.0	100	0.05		1987	-
Phosmet 732-11-6	EPA	Reduced body weight, liver cell vacuolation, inhibition of AChE	NOAEL: 2.0	100	0.02		1986	High
	WHO	Inhibition of AChE	NOAEL: 2.0	100	0.02		1979	-
Pirimiphos-Methyl 29232-93-7	EPA	Inhibition of AChE, human	NOAEL: 0.25	25	0.01	3	1986	High
	WHO	Inhibition of AChE, human	NOAEL: 0.25	10	0.03		1992	-
Prochloraz 67747-09-5	EPA	Increased SAP & liver weight, dog	NOAEL: 0.90	100	0.009		1988	High
	WHO	Increased liver weight	NOAEL: 1.3	100	0.01		1983	

(to be continued on the next page)

(continued)

Propargite 2312-35-8	EPA	No effects, dog. Reduced body weight in neonates, rabbits	NOAEL: 22.5	1000	0.02	8	1988	Medium
	WHO	Variable liver weight	NOAEL: 15	100	0.15		1982	
Propiconazole 60207-90-1	EPA	Gastric mucosal irritation, dog	NOAEL: 1.25	100	0.013	3	1988	High
	WHO	Proliferative liver changes	NOAEL: 4.0	100	0.04		1987	
2,4,5-T (2,4,5-trichlorophenoxy-acetic acid)	EPA	Increased urinary coproporphyrins	NOAEL: 3	300	0.01	3	1988	Medium
93-76-5	WHO	Decreased body weight gain	NOAEL: 3.0	100	0.03		1981	
Thiophanate-methyl	EPA	Decreased body weight	NOAEL: 8	100	0.08		1986	High
23564-05-8	WHO	Decreased body weight gain	NOAEL: 8.0	100	0.08		1977	
Thiram	EPA	Neurotoxicity	NOAEL: 5	1000	0.005		1987	Low
137-26-8	WHO	Hematological changes	NOAEL: 1.2	100	0.01		1992	-
Vinclozolin 50471-44-8	EPA	Organ weight changes, dog	NOAEL: 2.5	100	0.025	3	1986	High
	WHO	Organ weight changes	NOAEL: 7.2	100	0.07		1988	-
Zineb	EPA	Thyroid hyperplasia	LOAEL: 25	500	0.05		1986	Medium
12122-67-7	WHO	Effects on thyroid, dog	NOAEL: 50	1000	0.05		1980	-

[a] Source: U.S. EPA (1994) is the Integrated Risk Information System (IRIS) as of 1-1-94. Please note that data in IRIS can be updated on a monthly basis; thus, information in this table may be out of date. Please call the Risk Information Hotline at USA-513-569-7254 for more information. WHO values are taken directly from the latest evaluations of this group. The critical effect is listed for the rat unless another species is indicated.

[b] Ratios are rounded to one digit. We are not assuming any distribution of these differences.

[c] JMPR: Joint FAO/WHO Meeting on Pesticide Residues.

[d] AChE: Acetylcholinesterase.

ratios lie between 30- and 300-fold apart, and one ratio is 700-fold apart (for bromomethane). This large value reflects a fundamental difference in the approach to the risk assessment for this chemical. EPA relied on the toxicity to bromomethane directly; WHO considered the toxicity to the bromide ion.

A number of other analyses could be done with these data. For example, the development of the ADI is older than the corresponding RfD in 36 cases; the RfD is older than the corresponding ADI in 25 cases; and for 4 cases these values are developed in the same year. Forty-one RfDs are lower than corresponding ADIs; 6 ADIs are lower than corresponding RfDs; and 18 assessments are the same. The average RfD is lower than the average ADI.

DISCUSSION

The majority of ratios of ADI to RfD (i.e., 38 out of 65) are similar, that is within 3-fold. This is not unexpected. Expert groups often are reviewing the same underlying toxicity data and the methods that WHO and EPA use to estimate their respective values are similar. Another 20 comparisons of ADI to RfD lie between 3- and 30-fold of each other. Such differences are not large but may be of some concern. However, seven comparisons are beyond a 30-fold range in value, suggesting differences that warrant investigation.

One reason for these large differences may be that a number of organophosphate pesticides were evaluated based on the acetyl cholinesterase inhibition in humans. WHO and EPA have stated that wherever adequate human data are available, they should be used. Furthermore, acetyl cholinesterase inhibition is a sensitive, reversible, biochemical indicator of exposure which justifies the use of a smaller safety factor in the opinion of WHO (1990), but not necessarily EPA. These principles were applied in the evaluation of ADIs for dichlorvos, dimethoate, malathion, methamidophos, methyl parathion and pirimiphos-methyl. With malathion and piriphos-methyl, EPA also used human data, hence the RfDs are similar to the corresponding ADIs. With the others, EPA used animal data resulting in much smaller RfDs.

DDT (a 40-fold difference in ADI to RfD) is another case where WHO used a smaller SF than EPA based on the choice of a long-term exposure of large numbers of humans without any observable adverse effects. EPA's RfD was based on chronic animal toxicity data and used a correspondingly larger UF. However, a recent report (Wolf *et al.*, 1993) of possible risk of increased breast cancer among women with higher levels of DDT in the body might suggest that DDT should be reevaluated when this question is resolved.

With bromomethane, there is a 700-fold difference between the ADI and the RfD. WHO (1966) evaluated this fumigant on the basis of four studies in rats, and one each in rabbits and dogs. All animals were given feedstuffs fumigated with bromomethane at different concentrations. No treatment-related effects were seen. The ADI was based on bromide ion (the breakdown product of this fumigant) which had an ADI of 1 mg/kg (WHO, 1966). On the other hand, EPA used the findings of hyperplasia in the forestomach of rats given the chemical by gavage. This remarkably large difference between ADI and RfD definitely merits re-evaluation: WHO might look into possible reaction products between this fumigant and foodstuffs; EPA might look into the relevance of epithelial hyperplasia of the forestomach in rats given an irritant chemical by gavage. WHO stated in its document (1990) that "severe local effects may interfere with the interpretation of data, e.g.,

the production of forestomach epithelial hyperplasia and papilloma formation following administration of gastric irritants."

As with any endeavor based on expert judgment, differences may exist solely due to different judgment. This should be expected and perhaps desirable, since such judgments are complex and much room exists for individual interpretation and emphasis. However, as organizations strive to harmonize risk assessment methods during the next decade, it will be necessary to more closely scrutinize each others' assessments. Large differences in assessments should be questioned. For example, from our analysis, we would suggest that EPA investigate WHO's assessment of methamidiphos. WHO's value is more recent and is based on human information. Likewise, WHO should look into EPA's assessment for bromomethane. EPA's value is more recent and is based on the "parent" compound.

We recognize that these evaluations of WHO and EPA (and their associated justifications and caveats) are often only one starting point in the development of a comprehensive risk assessment. Sometimes, however, these evaluations and those of other health organizations are used in absentium of other critical information, such as exposure assessment or effects on other nonhuman systems. Moreover, it is important to understand differences in these ADIs and RfDs when they exist and to make sure that such differences are based on objective scientific judgments and not the lack of appropriate and relevant data.

As a proactive way to avoid such differences in the future, expert review groups could easily choose to read other existing evaluations ahead of their assessment meetings, and notify the other expert groups afterwards of a different judgment if it occurs. Such proactive practice occurs to some extent during current WHO meetings. However, as the number of scientists with risk assessment expertise grows and countries strive to develop their own capabilities, more not less disagreement may occur.

Computerized information systems, such as EPA's IRIS, may make this proactive review task somewhat easier, since EPA's latest evaluations are all in one location and the data base is relatively accessible. WHO and other expert review groups might consider the construction of computer systems similar to EPA and make them readily available to each other. This would assure better understanding of evaluations among groups, and perhaps lead to more consistency in these important risk assessment evaluations.

REFERENCES

Barnes, D. G. and Dourson, M. L. (1988). Reference dose (RfD): description and use in health risk assessments. *Regul. Toxicol. Pharmacol.* **8**, 471-486.

Dourson, M. L. and Stara, J. F. (1983). Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol.* **3**, 224-238.

International Programme on Chemical Safety (IPCS) (1994). *The Derivation of Guidance Values for Health-Based Exposure Limits.* Geneva, Switzerland. (in press)

Lu, F. (1988). Acceptable daily intake: inception, evolution and application. *Regul. Toxicol. Pharmacol.* **8**, 45-60.

Lu, F. C. and Dourson, M. L. (1992). Safety/risk assessment of chemicals principles, procedures and examples. *J. Occup. Med. Toxicol.* **1**, 321-335.

Lu, F. C. and Sielken, R. L. (1991). Assessment of safety/risk of chemicals: Inception and evolution of the ADI and dose-response modeling procedures. *Toxicol. Lett.* **59**, 5-40.

U.S. EPA (1994). *Integrated Risk Information System (IRIS).* Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

WHO (1966). Evaluation of some pesticide residues in food. *WHO/Food Add./67.32.* Geneva, Switzerland.

WHO (1990). Principles for toxicological assessment of pesticide residues in food. *Environmental Health Criteria 104.*

WHO (1994). *Summary of Toxicological Evaluations Performed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).* Geneva, Switzerland.

Wolf, M. S., Toniolo, P. G., Lee, E. W., Rivera, M., and Dubin, N. (1993). Blood levels of organochlorine residues and risk of breast cancer. *J. Natl. Cancer Inst.* **85**, 648-652.

(Received November 1, 1994 Accepted November 23, 1994)