UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
RESEARCH AND DEVELOPMENT

J. Routt Reigart, M.D.
Chair
Children's Health Protection Advisory Committee
MUSC Children Services
171 Ashley Ave.
Charleston, SC 29425

Dear Dr. Reigart:

This is in response to your letter dated September 15, 1999, as Chair of the Children's Health Protection Advisory Committee (CHPAC) on the subject of the proposed revisions to the Agency's Guidelines for Carcinogen Risk Assessment. Your letter includes the CHPAC's preliminary comments on the overall process for integrating new and improved science into the Environmental Protection Agency's (EPA) cancer risk assessment guidelines.

As you are aware, the Risk Assessment Forum's Technical Panel has been hard at work incorporating many of the public and Science Advisory Board (SAB) recommendations into the revised Guidelines and I am pleased that the CHPAC has chosen to recognize the considerable investment that the Agency has made in organizing two SAB meetings this past year and in producing additional guidance related to children. Presently, the Agency is awaiting the recommendations of the Science Advisory Board from their July review of this additional guidance. You correctly point out, in keeping with the SAB's earlier statements, that the Agency must continue to make decisions and improvements in its decision-making processes without answers to every question that needs to be asked and it is essential to capture those questions and institutionalize them into a regular process that stimulates, encourages and even requires the application of ongoing learning. Until we receive the SAB's recommendations from the July review, we do not know whether the SAB feels another review would be beneficial or whether the Agency would request one. Once we receive the SAB's comments, the Agency will decide which recommendations can be incorporated into the Guidelines at this time and which one's will require future guidance development as the science and our experience in applying the Guidelines evolves. As has been the Agency's practice with other guidelines, supplementary guidance will be developed that addresses unresolved issues. Your recommendation that the Carcinogen Risk Assessment Guidelines identify those issues as the subject of further work will be adopted. Similar discussions have been included in the preamble to other guidelines. Likewise, the Guidelines will inform the public about EPA's ongoing and planned research efforts to reduce uncertainty in assessing risk to children.

Finally, you requested information on the Agency's experience with making decisions about the use of linear versus nonlinear approaches to risk quantification. The proposed 1996 Guidelines have been applied in parallel with the 1986 Guidelines to 14 chemicals (Enclosure 1). added to the Integrated Risk Information System (IRIS). Hazard characterizations including narratives have been developed along with classifications done in accordance with the 1986 scheme. Likewise, in cases where quantification of cancer risk has been appropriate, unit risks were calculated using the linear multistage approach (LMS) under the 1986 Guidelines and the 2-step approach described in the proposed revised Guidelines. Resultant unit risks differences were minor. Each of these assessments has been peer reviewed by scientists external to EPA and all are available on the IRIS website. In none of the 14 cases were there sufficient mode of action information to warrant departure from the linear, nonthreshold approach to quantification.

During the same period, the Office of Pesticides Programs (OPP) referred a number of chemicals, including vinclozolin, chlorothalonil and alachlor to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) for review. In these three cases, OPP believed that the available data indicated a nonlinear mode of action. In the case of vinclozolin, the SAP concluded that the data were insufficient to establish the carcinogenicity potential of vinclozolin and recommended using a noncancer endpoint for the risk assessment. For alachlor, the SAP agreed with OPP's conclusions that sufficient data existed to describe the mode of action and that a nonlinear, margin of exposure (MOE) approach would be appropriate. In the case of chlorothalonil, the SAP concluded that a nonlinear mode of action was plausible and likely to be valid but that data gaps continued to exist. Reregistration Eligibility Decisions have been published for alachlor and chlorothalonil. Each of these assessments explicitly considered the possibility of differential susceptibility of infants and children to the toxic effects of pesticide residues. In each case, the risk assessments included both the linear nonthreshold approach and the MOE approach. For chlorothalonil, EPA concluded, in line with the SAP recommendation, that additional work was needed to confirm the validity of the nonlinear mode of action and, therefore, the regulatory decision for chlorothalonil was based on the linear approach. In the case of alachlor, even though the SAP had supported the Agency's conclusion of a nonlinear mode of action, OPP concluded that even under the assumption of linearity the dietary risks were in the acceptable range.

In addition to the three pesticides discussed above, the OPP Cancer Peer Review Committee (CPRC) and the Hazard Identification Assessment Review Committee (HIARC) have applied the proposed 1996/1999 Guidelines to approximately 40 cases. Enclosure 2 provides a list of these pesticides and the decisions reached by the CPRC and HIARC. OPP is continually updating this list and should be consulted directly for the most current information.

Regarding pending actions, the SAB reviewed the Office of Water's assessment for chloroform in October 1999 and it is anticipated that the report from that review will be issued in the near future. Secondly, the SAP will be rescheduling a review of OPP's draft hazard characterization of atrazine that was postponed due to inclement weather. Finally, the Agency in partnership with the National Institute of Environmental Health Sciences is organizing a small workshop entitled, "Information Needs To Address Children's Cancer Risk." The main focus of the workshop will be to address issues that have arisen during reviews of the proposed revised

Cancer Guidelines. The invited participants will be representative of the pediatric, toxicologic, and risk assessment community who are opinion-leaders in the area of human health testing, research, and assessment. After these activities, the Agency will take stock of what has been learned and will meet with the CHPAC's Science Work Group to discuss these experiences.

In closing, thank you for your interest in the ongoing revisions to the Cancer Guidelines and we look forward to a continuing dialogue with the Children's Health Protection Advisory Committee.

Sincerely,

Norine E. Noonan

Norine E. Noonan, Ph.D
Assistant Administrator

Enclosure (2)

Enclosure 1

Integrated Risk Information System Chemicals*

Acetonitrile
Barium and Compounds
Bentazon
Benzene
Beryllium and Compounds
Chlordane
Chromium III, Insoluble Salts
Chromium VI
Cumene
Ethylene Glycol Monobutyl Ether
Methyl Methacrylate
Methylene Diphenyl Diisocyanate
Naphthalene
Tributyltin Oxide

* Proposed 1996 Guidelines applied in parallel with the 1986 Guidelines.

Enclosure 2

Office of Pesticide Programs List of Chemicals Evaluated for Carcinogenic Potential

December 2, 1999

CHEMICAL	CURRENT OPP CLASSIFICATION AND DATE OF CLASSIFICATION	TUMOR TYPE / SPECIES	POTENCY Q* VALUE	CRAVE CLASS
99,263 S No. 11431-32-9 A Chem Code: 129171	Not Likely (2/11/97)			
hlor S No. 15972-60-8 A Chem Code: 090501	Likely (high doses); Not likely (low doses) (2/5/97)	Increased incidences of malignant & combined benign/malignant multiple tumor types in both sexes; Long Evans rat		
ents: HCPRC recommended that a non-linear MOE approach be used for the purpose of risk assessment. The consensus of the HCPRC was that MOEs for both the malignant mixed gastric tumors and the nasal adenomas be presented for a risk management decision.				
enidin S No. 68049-83-2 A Chem Code: 119016	Data are inadequate for an assessment of human carcinogenic potential (7/14/99)			
ents: Some of the CARC members considered the rat thyoid tumors to be treatment-related whereas an equal number of the CARC did not consider these tumors treatment-related. Thus under the Agency's Draft Cancer Risk Assessment Guidelines (July, 1999), the second group thought that the overall classification was "Not likely to be carcinogenic to humans." After some discussion, the CARC agreed that the consensus classification should be into the "Data are inadequate" category but no additional cancer studies were needed nor would there be any quantification of human cancer risk. However, the CARC recommended that an in vivo mouse micronucleus assay be conducted because of the observed effects on the hematopoietic system.				
ystrobin S No. 131860-33-8 A Chem Code: 128810	Not Likely (11/7/96)			
liocarb S No. 22781-23-3 A Chem Code: 105201	Not likely (10/2/97)			
xacor S No. 98730-04-2 A Chem Code: 911508	Cannot be determined but suggestive (2/12/97)	Increases in glandular stomach (forestomach) tumors in both sexes of mice and rats; CD-1 & Sprague-Dawley rats		
ents: HCPRC recommended that for risk assessment purposes, an MOE approach should be used based on the most sensitive precursor stomach lesion.				
ulide S No. 741-58-2 A Chem Code: 009801	Not likely to be a human carcinogen (5/20/99)			
chlor (Machete) S No. 23184-66-9 A Chem Code: 112301	Likely (11/4/98)	Multiple tumors in multiple sites in Sprague-Dawley rats including rare stomach tumors in F, rare kidney tumors in M & F, as well as tumors of the nasal mucosa and thyroid glands in M & F.		
ents: For the linear low-dose (Q1*) approach, extrapolation of risk should be based on the occurrence of renal cortical cell tumors in both sexes of rats at all dose levels tested. For the non-linear, margin of exposure (MOE) approach, extrapolation of risk should be based on the stomach, nasal and thyroid tumors in rats.				

CHEMICAL	CURRENT OPP CLASSIFICATION AND DATE OF CLASSIFICATION	TUMOR TYPE / SPECIES	POTENCY Q* VALUE	CRAVE CLASS
Chlorfenapyr (Pirate) CAS No. 122453-70-0 EPA Chem Code: 129093	Cannot Be Determined - Suggestive (9/25/96)	The overall evidence in animals was not persuasive, but could not be dismissed. Increased in tumors in rats occurred with significant positive trends only, and mainly at the highest dose.		
Chlorothalonil CAS No. 1897-45-6 EPA Chem Code: 081901	Likely (6/11/97) 3 (IARC)	Renal adenomas & carcinomas, both sexes of rats & mice; rarity of the tumor response in the kidney; papillomas and/or carcinomas of the forestomach in rats & mice; CD-1 mice; Fischer 344 & Osborne-Mendel rats.	7.66 E-3 (3/4)	Pending
Comments: HCPRC recommended that a non-linear appraoch to risk assessment, using MOE, should be used.				
Cyclanilide CAS No. 113136-77-9 EPA Chem Code: 026201	Not likely (4/7/97)			
Diazinon CAS No. 333-41-5 EPA Chem Code: 057801	Not likely human carcinogen (3/4/99)			
Dicrotophos (Bidrin) CAS No. 141-66-2 EPA Chem Code: 035201	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (7/21/99)	Increasing trend for thyroid follicular cell adenomas; C57BL/10 J CD-1 Alpk mice (M & F)		
Comments: CARC recommended that an in vivo comet assay on the target organ be conducted to examine possible interaction with DNA. The Committee recommended that for human risk characterization no quantification for cancer risk is required.				
Diflufenzopyr-sodium CAS No. 109293-98-3 EPA Chem Code: 005107	Not likely (9/24/98)			
Comments: The HIARC had a metabolism concern for 3,5-difluoroaniline (DFA), a rat metabolite. The HIARC concluded that if significant secondary residues [meat/milk] of this minor rat urinary metabolite [<1%] occurred, then the metabolite would have to be regulated based on carcinogenicity of dichloroaniline [DCA]. Since there are no toxicological data for DCA, as per HED policy, all chloroanilines are considered to be carcinogens and a carcinogenic risk assessment will be conducted using the Q1* for Parachloroaniline (PC). The Q1* is 6.38 x 10E-2.				
Diuron CAS No. 330-54-1 EPA Chem Code: 035505	Known/Likely (12/8/96)	Urinary bladder carcinomas; Wistar rat (M & F). Mammary gland carcinomas; NMRI mice (F). Information from structurally related analogs provided further support.	1.91 E-2 (3/4)	
Comments: For the purpose of risk characterization, a low dose linear extrapolation model to be applied to the animal data for the quantification of human risk, based on urinary bladder carcinomas in the male rat.				
Emamectin CAS No. 137512-74-4 EPA Chem Code: 122806	Not likely (2/26/98)			
Comments: This classification was based on the lack of evidence of carcinogenicity in male & female rats or male & female mice at doses that were judged to be adequate to assess the carcinogenic potential of the chemical.				

CHEMICAL	CURRENT OPP CLASSIFICATION AND DATE OF CLASSIFICATION	TUMOR TYPE / SPECIES	POTENCY Q* VALUE	CRAVE CLASS
Ethametsulfuron CAS No. 97780-06-8 EPA Chem Code: 129091	Can not be evaluated (9/12/98)			
Comments: The carcinogenic potential of Ethametsulfuron can not be evaluated since the highest dose tested in mice and rats did not elicit systemic toxicity and thus were judged to be inadequate to assess the carcinogenic potential of Ethametsulfuron. No rationale was provided for dose selection. HIARC noted that Ethametsulfuron, sulfonylurea is structurally related to other sulfonylureas such as Bensulfuron methyl, Halosulfuron methyl (Group E), Nicosulfuron (Group E), Primisulfuron methyl (Group D) & Rimsulfuron (Group E).				
Ethoprop (Ethoprophos) CAS No. 13194-48-4 EPA Chem Code: 041101	Likely (4/1/98)	Pheochromocytoma - adrenal glands (malignant); Sprague-Dawley rat rat (M); Cell carcinomas - thyroid gland; Sprague-Dawley & Fischer 344 rat (M); Evidence of clastogenicity.in vitro mutagenicity testing.	2.81 E-2 (3/4)	
Comments: A liner low-dose approach for human risk characterization & extrapolation should be based on malignant pheochromocytomas of the adrenal glands in male rats at all dose levels tested.				
Fenoxycarb CAS No. 72490-01-8 EPA Chem Code: 125301	Likely (12/12/97)	Lung adenomas, carcinomas & combined adenoma/carcinoma; Harderian gland adenomas; CD-1 mice (M).		
Comments: HCPRC recommended a low dose extrapolation model be applied to the animal data for the quantification of human risk.				
Fenpryroximate CAS No. 134098-61-6 EPA Chem Code: 129131	Not likely (8/22/96)			
Fluroxypyr (DOWCO 433) CAS No. 69377-81-7 EPA Chem Code: 128959	Not likely (1/6/98)			
Fluthiacet-methyl (Action) CAS No. 117337-19-6 EPA Chem Code: 108803	Likely (10/14/98)	Pancreatic cell tumors (exocrine adenomas, islet cell adenomas, and combined islet cell tumors); Sprague-Dawley rats (M). Hepatocellular tumors (adenomas and combined adenoma/carcinoma); CD-1 mice (M & F).	2.07 E-1 (3/4)	
Comments: CARC recommended a linear low-dose approach (Q1*) for human characterization & determined that extrapolation should be based on the combined hepatocellular adenoma/carcinoma in male mice. Although both tumor types (pancreatic cell & hepatocellular) are of concern, the hepatocellular tumors were selected for extrapolation since this tumor type was observed at a lower dose (10 mg/kg/day) in mice compared to the pancreatic cell tumors which were seen at a higher dose (130 mg/kg/day) in rats.				
HOE 107892 CAS No. 135590-91-9 EPA Chem Code: R47618	Not likely to be a human carcinogen (10/13/98)			
Halosulfuron-methyl CAS No. 100784-20-1 EPA Chem Code: 128721	Not likely (2/10/98)			

CHEMICAL	CURRENT OPP CLASSIFICATION AND DATE OF CLASSIFICATION	TUMOR TYPE / SPECIES	POTENCY Q* VALUE	CRAVE CLASS
Iprodione (Glycophene) CAS No. 36734-19-7 EPA Chem Code: 109801	Likely (11/19/97)	Hepatocellular tumors (M&F); Ovarian luteomas (F); CD-1 mice. Testicular interstitial cell tumors (Leydig cell); Crl:CD(SD)BR rats (M).	4.39 E-2 (3/4)	
Comments: CARC re-affirmed that the current linear low-dose extrapolation should be based on the liver tumors in both sexes of mice & the Leydig cell tumor in male rats.				
Isoxaflutole CAS No. 14112-29-0 EPA Chem Code: 123000	Likely (5/14/97)	Statistically significant increases in liver tumors in both sexes of mice & rats; statistically significant increases in thyroid tumors in male rats; CD-1 mice and Sprague-Dawley rats.		
Comments: For the purpose of risk characterization, a non-linear approach-MOE to be applied to the most sensitive precursor lesion in M rat thyroid, and that a linear low-dose extrapolation to be applied for the tumors of the rat liver.				
Kresoxim-methyl CAS No. 143390-89-0 EPA Chem Code: 129111	Likely to be carcinogenic to humans (3/17/99)	Liver tumors (hepatocellular adenomas, hepatocellular carcinomas & combined adenomas/carcinomas); Wistar rats (M & F).	2.90 E-3 (3/4)	
Comments: For human risk characterization, CARC recommended the extrapolation of risk using the linear low-dose (Q1*) approach based on combined hepatocellular adenomas/ carcinomas in female rats. This extrapolation was supported by the lack of confirmation of the mode of action for liver tumor induction & dose-dependent increased incidence of liver tumors in male & female rats.				
MON 13900 (Furilazole) CAS No. 121776-33-8 EPA Chem Code: 911596	Likely to be carcinogenic to humans (6/19/99)	Multiple tumors were seen at multiple sites in two species including both benign & malignant liver tumors in M & F Sprague-Dawley rats & CD-1 mice, rare tumors such as stomach & testicular tumors in M rats & lung tumors in both sexes of mice.	8.22 E-2 (3/4)	
Comments: CARC also recommended for human risk characterization, the extrapolation of risk using the linear low-dose (Q1*) approach for most potent & biologically significant tumor type was recommended. This extrapolation was supported by the increases in the incidence of liver, stomach & testicular tumors as well as lung tumors in one or both sexes of rats or mice, the potential for clastogenic effect, lack of adequate genotoxicity/mutagenicity data, as well as lack of mode of action. MON 13900 is structurally-related to alachlor & acetochlor, which cause tumors at multiple sites (liver, stomach, or lung) in rats and/or mice and have been classified by the CARC as "likely to be carcinogenic to humans."				
Methomyl CAS No. 16752-77-5 EPA Chem Code: 090301	Not likely (9/5/96)			
Oxamyl (Vydate) CAS No. 23135-22-0 EPA Chem Code: 103801	Not likely (8/15/96)			
Prallethrin (ETOC) CAS No. 23031-36-91 EPA Chem Code: 128772	Not likely (9/2/99)			
Propachlor CAS No. 1918-16-7 EPA Chem Code: 019101	Likely (7/30/97)	Multiple tumors/multiple sites; Rare stomach tumor; Fischer 344 rat (M); Thyroid tumors & granulosa/theca cell tumors; Sprague-Dawley rats (M & F). Hepatocellular tumors; CD-1 mice (M).		
Comments: A linear low-dose approach for human risk characterization & extrapolation of risk should be based on both neoplastic [ovarian tumors (rats) & liver tumors (M mice)] & non-neoplastic (liver hypertrophy (mice) lesions.				

CHEMICAL	CURRENT OPP CLASSIFICATION AND DATE OF CLASSIFICATION	TUMOR TYPE / SPECIES	POTENCY Q* VALUE	CRAVE CLASS
Propetamphos CAS No. 31218-83-4 EPA Chem Code: 113601	Not likely (9/16/98)			
Pyrethrins CAS No. 121-21-1 EPA Chem Code: 069001	Likely (2/3/99)	Liver tumors (F); Thyroid tumors (M & F); Charles River CD rats	5.14 E-3 (3/4)	
Spinosad (XDE-105) CAS No. 131929-60-7 EPA Chem Code: 110003	Not likely (4/30/97)			
Sulfosulfuron (MON 31500) CAS No. 141776-32-1 EPA Chem Code: 085601	Likely (8/26/98)	Rare transitional cell papilloma & carcinoma of the urinary bladder in females; Sprague-Dawley rats. Rare mesenchymaltumors of the urinary bladder in male as well as renal adenomas in male and female mice; CD-1	1.03 E-3 (3/4)	
Comments: The Committee recommended that a linear low-dose approach (Q1*) for human risk characterization and extrapolation of risk should be based on the incidence of benign mesenchymal tumors in male mice. This extrapolation, rather than an MOE approach, is warrented due to lack of data on mode of action.				
Thiabendazole CAS No. 148-79-8 EPA Chem Code: 060101	Likely to be carcinogenic to humans (5/26/99)	Thyroid follicular cell adenomas and combined adenomas/carcinomas; Sprague-Dawley Crl:CD BR rats		
Comments: CARC recommended an MOE approach for the quantification of human cancer risk. This extrapolation is supported by the weight-of-the evidence which suggests that Thiabendazole may interfere with thyroid-pituitary homeostasis.				
Thiafluamide (FOE 5043) CAS No. 142459-58-3 EPA Chem Code: 121903	Not likely (1/22/97)			
Thiophanate-methyl CAS No. 23564-05-8 EPA Chem Code: 102001	Likely to be carcinogenic to humans (4/28/99)	Hepatocellular adenomas (M & F); Combined adenomas, carcinomas and/or hepatoblastomas (M); CD-1 mice. Thyroid follicular cell adenomas (M & F); Thyroid follicular cell carcinomas as well as combined adenomas and/or carcinomas (M); F344 rats.	2.08 E-3 (3/4)	
Comments: For human risk characterization, CARC recommended the extrapolation of risk using the linear low-dose (Q1*) default approach for liver tumors. This extrapolation was supported by the lack of confirmation of the mode of action, concern for mutagenicity & dose-dependent increases in the incidence of liver tumors in male and female mice.				
Tralkoxydim CAS No. 87820-88-0 EPA Chem Code: 121000	Likely (7/8/98)	Benign Leydig cell tumors at all dose levels with the incidences at the high dose exceeding the concurrent & historical control; Wistar rats (M).	1.68 E-2 (3/4)	
Comments: Committee recommended that a linear low-dose (Q1*) for human risk characterization & extrapolation of risk should be based on the occurrence of Leydig cell tumors of the testes in male rats at all dose levels.				

CHEMICAL	CURRENT OPP CLASSIFICATION AND DATE OF CLASSIFICATION	TUMOR TYPE / SPECIES	POTENCY Q* VALUE	CRAVE CLASS
Tribufos (Tribuphos/DEF) CAS No. 78-48-8 EPA Chem Code: 074801	Likely (high doses); Unlikely (low doses) (1/8/97)	Liver (hemangiosarcoma) (M), Lung (alveolar/bronchiolar adenoma) (F), Small intestine (adenocarcinoma) (M & F); CD-1 mice.	2.39 E-1 (3/4)	
Comments: A non-linear approach (MOE) using the most sensitive toxic endpoint considering all species tested was recommended for the purpose of risk characeterization.				
Trichlorfon (Trichlorphon) CAS No. 52-68-6 EPA Chem Code: 057901	Not likely to be carcinogenic at low doses, but likely to be carcinogenic at high doses (2/17/99)	Tumors of the kidneys (adenomas) in male F344 rats & tumors of the lungs in both sexes (adenomas/carcinomas in M; carcinomas in F). Mammary tumors in female CD-1 mice.		
Comments: Tumors in rats and mice were observed at dose levels that were considered excessively toxic (Rats: increased mortality, ChE inhibition, non-neoplastic histopathological changes; Mice: increased mortality and ChE inhibition). None of the tumors was considered to be relevant for human risk assessment because they were seen only at doses that were excessively toxic.				
Triclosan (Irgasan) CAS No. 3380-34-5 EPA Chem Code: 054901	Not classifiable (3/10/98)			
Comments: The Committee was unable to assign a carcinogenicity classification to Triclosan, due to the lack of a second study in a second species.				
Troysan polyphase (IPBC) CAS No. 55406-53-6 EPA Chem Code: 107801	Not likely (9/18/96)			