Chuck Tuttle 4/24/84
Bill Buzhardt

Immediate Action.
See Ed's note. We discussed this at staff today.

cc: Anne Baker
Ed Thomson
Susan Stewart

APR 24 RECD

Quick — Have Phil draft RIB into part of this call M. OK

From the desk of

ED JOHNSON

4/19

John Melone

I met w/ Moore Hill and Dave. Will OK tolerance based on minor incremental exposure. Will reevaluate all tolerances in 1985 as part of the Regis. Std

In that regard, HED (over)

must determine data needs for residues or commodities contributing to high theoretical intake levels within the next week so we can get the data this year.

Doug has to get the letter out. He will also be clearing it with Dick Hill to assure agreement w/ HA.

Thanks Ed

cc Capt.

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Teratogenic Effects

Benomyl in/on Small Grains, Liver and Milk (PP 6F1748)

	for established tolerances (inc. milk at 0.1 ppm)	with addition of small grains and liver (at 4 ppm)	with addition of small grains, liver, and milk at 1.0 ppm
Risk of oncogenicity*	7.5×10^{-5}	7.62×10^{-5}	8.95×10^{-5}
MOS for reproductive effects**	213	209	178

MOS for teratogenicity*** (single small servings to a pregnant 60 kg woman)

milk (0.1 ppm)	—	75,000
milk (1.0 ppm)	—	7,500
liver (4.0 ppm)	—	2,650
wheat	—	150,000
oats	—	37,500
rye	—	150,000
barley	—	42,850

* based on mouse oncogenic study on MBC (metabolite)

* based on reproduction study with NOEL of 7.5 mg/kg/day

** based on an NOEL of 30 mg/kg/day (teratogenicity study)

Calculation of ADI and TMRC

ADI calculations are based on a 3-generation rat reproduction study with an NOEL of 100 ppm (or 5 mg/kg/day).

S.F. = 100

ADI = 0.05 mg/kg/day

MPI = 3.00 mg/day (60 kg person)

TMRC for established tolerances (inc. milk at 0.1 ppm	TMRC with addition of small grains and liver (at 4 ppm)	TMRC with addition of small grains, liver, & milk at 1.0 ppm
2.1139 mg/day (70.46 % of MPI)	2.1479 mg/day (71.60 % of MPI) an incremental increase of 1.6% (0.0340 mg/day) in the TMRC	2.5342 mg/day (84.47 % of MPI) an incremental increase of 19.9% (0.4203 mg/day) in the TMRC

Benomyl ADI — EPA Considerations

From the early 1970's until the early 1980's the ADI for Benomyl was based on a 2-year feeding study in dogs with an NOEL of 500 ppm (equivalent to 12.5 mg/kg/day). (Haskell Labs, #48-70, 3/7/70). [This is the same study that WHO found to be inadequate for the purpose of setting an ADI for Benomyl.] By applying a safety factor of 100, an ADI of 0.125 mg/kg/day was obtained. Also available since the early 1970's was a 3-generation rat reproduction study (Haskell Lab., #264-68, 11/18/68) with an (EPA) NOEL of 100 ppm (equivalent to 5 mg/kg/day). The following rationale was presented in a subsequent TB review (5/13/75) as to why the dog study, rather than the 3-generation rat study, was used to calculate the ADI.

"Since only adverse effect in rat reproduction is borderline, consisting of somewhat lower weanling weights in '500' and '2500 ppm' pups of the last 4 (of 7) litters, we can assign "no-effect level" for the dog, 12.5 mg/kg/day as that for the most sensitive species."

It should be noted that this same 3-generation rat reproduction was also later reviewed by WHO and it was determined by them to have a NOEL of 2500 ppm (i.e. the highest dose tested).

During the course of the RPAR proceedings on Benomyl during the early 1980's, EPA ~~selected~~ decided to change the study on which the ADI was (formerly) based and consequently the ADI also. The written record provides little information as to the rationale for this change. The 3-generation rat reproduction study, referred to earlier, with an (EPA) NOEL of 100 ppm (equivalent to 5 mg/kg/day) was used with a safety factor of 100 to calculate an ADI of 0.05 mg/kg/day. This is the ADI being used for Benomyl by EPA at the present time.

Benomyl ADI — WHO Considerations

The WHO did not have an ADI for Benomyl or for Carbendazim (MBC) prior to 12/83 because the toxicity data base for both chemicals (individually) was insufficient to support establishment of ADI's. In 1983, however, available toxicity data for both chemicals was combined and considered together and it was determined that sufficient data was available *in toto* to support ADI's for both chemicals. The rationale for the combining of data was that Benomyl, following administration to mammals, is rapidly and nearly completely metabolized to Carbendazim and the resultant toxicity for both chemicals is essentially the same both qualitatively and quantitatively (when appropriate adjustments are made for the differences in their molecular weights).

With respect to Benomyl *per se*, WHO determined that there was no adequate long-term study available for the purpose of assessing chronic toxicity and on which an ADI might be based. A 2-year chronic dog feeding study (Haskell Lab., #48-70, 3/4/70) with an NOEL of 500 ppm was judged inadequate for this purpose. A 3-generation rat reproduction study (Haskell Lab., #264-68, 11/18/68), with (WHO) NOEL of 2500 ppm, was not considered useful for this purpose, nor a 2-year chronic feeding study in rats with a NOEL of 2500 ppm (Haskell Lab, #232-69, 8/15/69). (7)

For carbendazim, however, an adequate 2-year dog study was available. The NOEL for this study was 100 ppm (equivalent to 2.5 mg/kg/day). Two separate long-term feeding studies in rats were also available for which the NOEL was determined to be 500 ppm (equivalent to 25 mg/kg/day). The more sensitive study in dogs was used to calculate the ADI for carbendazim by applying a 200 fold safety factor. A 200 fold safety factor, rather than 100, was used to due to uncertainties and/or incompleteness with respect to teratological studies performed on carbendazim (data for individual animals was lacking). Application of the 200 fold safety factor to the NOEL of 2.5 mg/kg/day from the dog study resulted in an ADI of 0.0125 mg/kg/day, which was rounded off to 0.01 mg/kg/day.

Due to the rapid conversion of Benomyl to carbendazim in mammals and the qualitative and quantitative similarities of the respective toxicities, the ADI for carbendazim (0.01 mg/kg/day) was used as a basis for calculating an ADI for Benomyl. This was done by adjusting for their different molecular weights. Since Benomyl has a MW approximately twice that of carbendazim, a dosage level of 0.01 mg/kg for carbendazim was judged to be equivalent,

on a molecular basis, to a dosage level of 0.02 mg/kg/day for Benomyl. Thus, an ADI of 0.02 mg/kg/day was established for Benomyl.

It should be noted that if the missing information on the teratological and other studies performed on carbendazim are supplied to WHO and the related concerns and uncertainties are resolved, then WHO will probably change the safety factor from 200 to 100. If this happens, the ADI for carbendazim would become 0.02 mg/kg/day and the ADI for benomyl would become 0.04 mg/kg/day.

Additional Data from Chaisson's TAS System

These calculations are based on the (EPA) ADI of 0.05 mg/kg/day.

"Prior" refers to all existing tolerances for benomyl including milk at [redacted] 0.1 ppm (liver at 0.2 ppm)

"New Action" refers to all existing tolerances for benomyl but with milk at 1.0 ppm (liver still at 0.2 ppm)

Subgroup	Prior	New Action
U.S. Population (all seasons)	[redacted]	[redacted]
% exceeding 100% of ADI	36%	43%
" " 200% " "	14%	17%
" " 500% " "	3%	3%
" " 1000% " "	0.4%	0.5%
Nursing Infants (< 1 year)		
% exceeding 100% of ADI	50%	51%
" " 200% " "	41%	45%
" " 500% " "	15%	10%
" " 1000% " "	2%	2%
Non-Nursing Infants (< 1 year)*		
% exceeding 100% of ADI	72%	94%
" " 200% " "	61%	76%
" " 500% " "	34%	42%
" " 1000% " "	9%	12%

*see attached for percent of intake from various sources.

(10)

Subgroup	Prior	New Action
Pregnant Females, Nursing		
% exceeding 100% of ADI	37 %	48 %
" " 200% " "	9 %	14 %
" " 500% " "	0	0
" " 1000% " "	0	0
Children (1-6 years)		
% exceeding 100% of ADI	69 %	83 %
" " 200% " "	49 %	59 %
" " 500% " "	17 %	11 %
" " 1000% " "	3 %	4 %
Children (7-12 years)		
% exceeding 100% of ADI	56 %	69 %
" " 200% " "	19 %	38 %
" " 500% " "	3 %	5 %
" " 1000% " "	0	0
Males (13-19 years)		
% exceeding 100% of ADI	33 %	44 %
" " 200% " "	9 %	13 %
" " 500% " "	<1 %	<1 %
" " 1000% " "	0	0
Females (13-19 years)		
% exceeding 100% of ADI	31 %	39 %
" " 200% " "	9 %	12 %
" " 500% " "	<1 %	<1 %
" " 1000% " "	0	0

Non nurs. infants (< 1 yr)

4 → 5 × ADI

.208 → .26

	Tolerance (ppm)	% of total exposure: oil .1%, flour .2%
soybeans	.2	= 20% of exposure
apples	7	= 25% " "
O.J.	10	= 15% " "
peaches	15	= 5% " "
pears	7	= >5% " "
pineapple	35	= 3% " "
apricots	15	= 2½% " "
rice	5	= 1.4%
tomatoes	5	= 3-4%
milk	1.0	= 23% } also on non-fat dry milk in milk base formula

87% of exposure out of 90 commodities

Note: ① Concentration of pesticide residue does not increase with drying of fruit
- stays with water soluble fraction
Therefore, does not migrate so much into oil. Consumption of oil contributes due to this.

Jean Davison
on 4/6/84