

US EPA ARCHIVE DOCUMENT

12-31-86



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

DEC 31 1986

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Linuron Special Review Comments of Risk Assessment

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12/31/86

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THRU: Reto Engler, Chief  
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Several substantive issues need to be resolved before the appropriate quantitative risk assessment procedures can be applied. As these issues are not yet resolved, it has been necessary to consider what changes, if any, need to be made to earlier EPA estimates based on two sets of assumptions. No comment is made below with reference to dietary risks as this step is accomplished by multiplying the dietary exposure estimate by the cancer potency estimate. Thus the problems for resolution are: a) determining the Linuron exposure associated with various individual food substances or raw agricultural commodities; b) determination of the cancer potency estimates. If the Agency accepts the registrants claim as to mechanism of action it may be reasonable to select the best fitting model. Otherwise, the issue of fitness of a mathematical model to rodent tumor rates observed in a standard two year feeding study or cancer study is not considered by EPA to be germane to the downward extrapolation of the observed values (to the region of low-dose exposure expected in human residues). It has been frequently shown that most of the standard approaches to mathematical modeling fit positive cancer bioassay data similarly in that none may reject the null hypothesis of lack of fit at  $p < .05$ . However, it is not possible to obtain a cost-effective cancer bioassay at the dose levels of interest, i.e., rates  $< .001$  or  $1/1,000$ , as the required sample size per dose level is prohibitive. The EPA

has therefore selected the multi-stage model approach to cancer and tumor induction as having the most biological validity in the absence of data which illustrate the mechanism of action for the subject chemical in inducing and/or promoting cancer. Thus the EPA estimates of cancer potency should be used if the mechanism of action arguments submitted by the registrant are rejected. Conversely the registrants figures should be accepted if the EPA is prepared to accept the registrants arguments as being scientifically valid.

Secondly, the virtually safe dose level of a chemical alluded to by the registrant also not germane to the OPP mission. The concept of a virturally safe dose for estimating a minimum concentration of the chemical which assures that the additional risk of cancer associated with that level of lifetime exposure to the subject chemical will not exceed some very low rate such as 1 per million ( $10^{-6}$ ) or 1 per hundred million ( $10^{-8}$ ) is the concern addressed by EPA when safe concentration in water or air are evaluated. But, in the Office of Pesticide Products upper bounds on risk are estimated for specific environmental exposures associated with use of the chemical for expected residues in or tolerances for dietary components.

Thirdly the company analysis of hyperplasia is not in agreement with our findings. The data in Table 2 of attachment 3 to the October 3, 1986 "Response to Special Review ..." is misleading in Table A below we show the DuPont figures and in Table B we show the additional tabulations needed to assess the additive effects of Linuron on the test histology:

TABLE A

	<u>Hyperplasia</u>			<u>Adenoma</u>	
	Event	Evaluable	Rate	Events	Rate
Control	1	68	.0147	4	.0588
50 ppm	5	56	.0893	9	.1607
150 ppm	4	64	.0625	19	.2969
625 ppm	6	66	.0909	37	.5606

TABLE B

	<u>Hyperplasia in Animals</u>			<u>Hyperplasia</u>		
	<u>Free of Adenomas</u>			<u>and/or Adenoma</u>		
	Event	Evaluable	Rate	Events	Evaluable	Rate
Control	1	64	.0156	5	68	.0735
50 ppm	5	47	.1064	14	56	.2500
150 ppm	2	45	.0444	21	64	.3282
625 ppm	6	29	.2069	43	66	.6515

If hyperplasia contributed no additional information one would expect little gain either by looking at the total event rate or from the subgroup who do not have more advanced disease. Adding the hyperplasias to the adenomatous animals has smoothed out the dose-response relationship and a highly significant,  $p < .01$ , dose response slope (Cochran-Armitage test) is observed for animals with hyperplasia but not more advanced disease.

We conclude that if the data are assumed to behave according to multistage cancer theory, the earlier EPA risk assessments are appropriate. If, however, the du Pont presentation on mechanism of action is acceptable, then their approach is acceptable.