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

MAR 7 1996

MEMORANDUM

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Comments on Third Carcinogenicity Peer Review of Alachlor

FROM: Kerry L. Dearfield, Ph.D.
Science Policy Council Staff (8103)
Office of Science Policy

TO: Stephanie R. Irene, Ph.D.
Division Director
Health Effects Division (7509C)
Office of Pesticide Programs

I agree with the Carcinogenicity Peer Review Committee's (CPRC's) final recommendation to utilize the Margin of Exposure (MOE) methodology for the estimation of human risk for Alachlor. However, I cannot fully concur with some of the underlying reasoning and conclusions found in the peer review document. My comments below will address just one main point, the mode of action in nasal tumors; other nonconcurrence items are relatively minor and too many to detail here. Please note I was not at the last CPRC meeting (January 3, 1996), as others were not, due to the government furlough at the time.

The CPRC document states that the nasal tumors are rat specific and not relevant for human cancer assessment. I am not convinced that this has been clearly demonstrated based on the available data. The discussion on pages 29 - 41 is relevant. While the data point to the Long-Evans rat as probably more sensitive than other tested animals to nasal tumors, it is not unique. For example, acetochlor, a structural analogue, produces nasal tumors in Sprague-Dawley rats, presumably via a similar mode of action. It can be argued that the rat is probably much more sensitive than other species to the action of alachlor (most likely due to its metabolites) via differences in metabolic rates between species. The generation of reactive metabolites is probably dose-related where adverse effects are seen at higher tested doses. Outside of quantitative differences, there is not a good qualitative argument to say a similar mode of action cannot occur in humans. These points direct one to the MOE approach with the nasal tumor NOEL of 2.5 mg/kg/day (1983 rat study) as a point of departure for human cancer assessment.

The mode of action of nasal tumor induction cannot rule out the possibility of other mechanisms. The suggested reactive

product, 2,6-diethyl-benzoquinonimine (DEBQI), has chemical reactivity and is suggested by the registrant to bind to macromolecules as protein to result in cytotoxicity and cell proliferation. Not mentioned is that the imine may be able to bind to other macromolecules as DNA and RNA; certainly its structural alert supports the reactivity. This binding may play a role in the induction of nasal tumors. The registrant submission (MRID #43369201) shows that there is qualitatively a low level of binding to nasal tissue DNA after an oral gavage to alachlor. The genetic activity of alachlor via its metabolites has been shown via registrant submissions and this supports a role for tumor induction once enough alachlor (or metabolite(s)) is present in nasal tissue. Several metabolites including 2,6-diethylaniline (a precursor to DEBQI) show some, albeit, weak activity in the Salmonella assay; it appears alachlor genotoxic activity is "gained" as it is converted to some metabolites (parent compound itself is negative in the Salmonella assay). Also, alachlor has been reproducibly shown to induce unscheduled DNA synthesis (UDS) after an *in vivo* exposure in rats. Acetochlor also induces a similar response for UDS *in vivo*. These points are consistent with the conclusion on mutagenicity and cell proliferation found on page 65. However, this comment memo suggests that there are other activities that may contribute to tumor induction. The document doesn't address even other additional possible activities, as chlorine displacement. These should not be ruled out so readily. Also, I am not totally convinced that this mode of action is not relevant to humans (the argument is quantitative, not qualitative - this is similar to the approach we took for Aliette and o-phenyl phenol). Therefore, the nasal tumors and other plausible modes of action, particularly the one discussed above, for the carcinogenicity evaluation of alachlor should be included in the risk characterization and adequate MOE for alachlor.

I wish I could add a lot more detail to the discussion above. I commented extensively on the draft before this final document. Most of my comments were addressed, but not enough for me to concur fully on this final. Since there is so little time to review the final and complete a detailed response before signatures are required, the above presents what I basically feel in broader strokes.