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March 27, 2003

Associate Director for Communications
Office of the Director
National Institutes of Health
Building 1, Room 344
9000 Rockville Pike
Bethesda, MD 20892

Subject: Request for Reconsideration of the Request for Correction Submitted by Chemical Products Corporation dated November 15, 2002
Information Quality Appeal

Dear Madam or Sir;

In NIH's letter to me dated March 19, 2003 signed by Dr. Christopher J. Portier, NIH essentially denied Chemical Products Corporation's (CPC's) Request for Correction filed under the Information Quality Act on November 15, 2002. NIH did not agree to withdraw the draft Technical Report 494 abstract now on the NTP website.

NIH promised to put additional information on the NTP website within approximately one month alerting the public to the fact that the Anthraquinone sample used in the TR494 study was contaminated with 9-nitroanthracene. We respectfully disagree that the promised additional statement to be added to the NTP website brings the information on the NTP website concerning NTP Technical Report 494 into compliance with the requirements of the Information Quality Act. The website will still contain information known to NIH to be incorrect, and the promised additional statement does not provide sufficient

information for the public to become immediately aware that other information on the website is incorrect. Therefore, CPC is submitting this Request for Reconsideration of our original Request for Correction.

The abstract for draft TR494 on the NTP website contains the statement, "Anthraquinone was mutagenic in Salmonella typhimurium strains TA98 and TA100 with and without S9 metabolic activation enzymes." This statement is now acknowledged by NIH to be incorrect; Anthraquinone is not a mutagen. This statement should be removed from the NTP website along with the conclusions contained in the abstract of draft TR494 which can no longer be considered to be scientifically valid. The peer review of draft TR494 can no longer be considered valid because the reviewers were told that the substance they were dealing with, Anthraquinone, was known to be a mutagen; in fact, Anthraquinone is not mutagenic.

Additional information which NIH adds to the NTP website should contain the specific statement that Anthraquinone is not mutagenic in Salmonella typhimurium strains T98 and TA100 with or without S9 metabolic activation enzymes. It should also contain the information that the identified contaminant of the Anthraquinone sample used in NTP's two-year study is recognized as being a mutagen, and that the particular Anthraquinone sample used by NTP has been tested and found to contain sufficient contaminants to make it mutagenic in Salmonella typhimurium strains T98 and TA100.

Dr. Portier's letter contains the statement that 2-hydroxyanthraquinone "is a strong mutagen". Unfortunately, NTP seems, once again, to be reporting possibly anomalous mutagenicity test results without first considering in detail earlier test results reported in the scientific literature.

We wish to alert NIH that 2-hydroxyanthraquinone has been reported in the literature to be non-mutagenic in TA98 with and without S9 metabolic activation enzymes, and non-mutagenic in TA100 without S9 metabolic activation enzymes. Very weak mutagenicity (about two-fold increase in number

of revertants) was found in TA100 with S9 metabolic activation enzymes (Tikkanen et al., Mutation Research, 116, 297-304 (1983)). Since 2-hydroxyanthraquinone was reported in TR494 to be excreted in the urine, only the mutagenicity results without S9 activation are relevant. Tikkanen et al. also found that 2-hydroxyanthraquinone was not mutagenic in TA2637 in the absence of S9 activation.

Ninety AQ derivatives and related anthracene derivatives were screened for mutagenicity with five Salmonella typhimurium tester strains with and without activation (Brown and Brown, Mutation Research, 40, 203-224 (1976)). Brown and Brown reported that, overall, mutagenicity was greater with NO_2 functional group addition than with OH functional group addition. This further calls into question the assertion in Dr. Poitier's letter that 2-hydroxyanthraquinone is "approximately 10-fold more potent [mutagen] than 9-nitroanthracene".

Our analysis of the Anthraquinone sample employed by NTP in the studies reported in TR494 found that the sample was not homogeneous and that there appeared to be more than one mutagenic contaminant. This information was submitted to Dr. Kenneth Olden in the fall of 2000. Specifically, when the sample was dissolved in concentrated sulfuric acid, discrete particles of insoluble matter were observed floating in the Anthraquinone solution. After removal of these insoluble impurities and reprecipitation of the Anthraquinone, the purified Anthraquinone was tested by two laboratories and found to contain no detectable 9-nitroanthracene. Mutagenicity was still observed in this purified NTP sample (less than observed in the "as received" NTP Anthraquinone sample, however). The dissolved and reprecipitated NTP sample was a "battleship gray" color rather than the pale yellow color of pure Anthraquinone. We believe that careful characterization of the NTP Anthraquinone sample is warranted, with careful attention given to the possibility that there are discrete particulate impurities present in the sample which may have also significantly affected the results of NTP's two-year study. We hope that NTP will screen a

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relatively large portion of this sample and perform separate analyses on the plus 16 mesh fraction, minus 16 mesh-plus 30 mesh fraction, minus 30 mesh-plus 50 mesh fraction, and minus 50 mesh fraction.

In summary, we request reconsideration of NIH's decision to leave incorrect information contained in the abstract of draft TR494 on the NTP website. We do not believe that the statement which NIH has promised to add to the NTP website within approximately one month fully characterizes or specifically identifies to the public the incorrect information contained in the abstract of draft TR494. We, once again, request that the abstract of draft TR494 be immediately withdrawn because the information contained in it does not meet the requirements of OMB's Information Quality Guidelines.

We are grateful that NIH has committed to adding a statement that the sample of Anthraquinone used in the two-year NTP study was contaminated. We ask that a statement that Anthraquinone is not mutagenic to Salmonella typhimurium strains T98 and TA100 with or without S9 metabolic activation enzymes be added to the website as soon as possible, and that the sample of Anthraquinone used in the two-year NTP study be characterized in a statement on the website as being contaminated with at least one mutagenic contaminant in sufficient quantity to yield positive results for mutagenicity in TA98 and TA100 with and without S9 activation.

If I can answer any questions concerning this letter or provide further information, please telephone me at 770-382-2144.

Sincerely,

/s/

Jerry A. Cook
Technical Director