

- - CONFIDENTIAL

CONFERENCE AT KETTERING LABORATORY

PRESENT: R. R. Suskind M.D. - Kettering Laboratory
Cincinnati, Ohio
H. Oettel M.D. - B.A.S.F. Ludwigshaven,
Germany
E. P. Wheeler - Monsanto
L. C. Weger - Monsanto

This conference was arranged to share information between Badische, Monsanto and the Kettering Laboratory on chlor-acne. In the case of both Badische and Monsanto, the incident of chlor-acne followed the violent decomposition of a batch of trichloro-phenate in process. The Monsanto incident occurred March 8, 1949 and the German incident in December, 1953. Both cases were followed in a period of days or weeks by an outbreak of chlor-acne of epidemic proportions.

Following the Monsanto incident Dr. Suskind and the Kettering Laboratory have done extensive studies into the problem. Dr. Suskind reviewed, in some detail, work and studies which were carried out. In the beginning, Dr. Suskind related tests and studies made on four of the more severe acne cases and presented pictures of the individuals involved together with photo micrographs of skin biopses showing acne lesions. Dr. Oettel presented similar photographs and photo micrographs of German cases which compared very closely with those from Monsanto. It appeared that the German cases may have been more severe with regard to the skin disturbances. It was also apparent that the residual scarring was a good deal more pronounced.

Dr. Suskind described in some detail, animal tests continued by skin application and by inhalation using both sodium TCP and 245T on a

CONFIDENTIAL

015582

variety of animals including rabbits, rats (adult and baby), cats, dogs and guinea pigs, etc. While in many of the experimental animals evidence of toxicity was manifest, there was no chlor-acne developed. Dr. Suskind and Dr. Oettel both agreed that the so called "rabbit ear test", as developed and described by Messrs. Adams, Irish, Spencer and Rowe, is unrealistic and non-reproducible. Since none of the very extensive animal experiments were successful in the production of acne, a decision was made to employ human volunteers in an attempt to find a means of evaluating the acnegenic potential of various process materials.

In the first of these experiments, Halowax 1014 (a known acnegen) was chosen as a control. This was applied as a 20% application in "plastibase" an ointment essentially consisting of 5% Polyethylene in mineral oil. Halowax in this experiment was compared to 245T and both materials were applied to the forearm of the human volunteers and kept in contact with the forearm on a continuous basis. Extensive liver function tests were conducted every other day and the volunteers were examined daily by a qualified physician who was particularly mindful of possible liver changes. In 2 to 3 days, redness developed in the Halowax exposures and in 10 days there were some follicular changes terminating in actual lesions. There was no evidence of skin changes in the 245T exposures. Acne was produced only locally in the sight of exposure in every case, that is, there was no systemic change. (At other hospitals with large scale tests, using Halowax, acne was produced in all cases except people above the age of 70. In no case was there any change in liver functions.)

CONFIDENTIAL

C15583

In a later series of experiments, Dr. Suskind described how three materials submitted by Monsanto were compared with Halowax using the technique described above. The materials from Monsanto were all sodium triphenolate prepared as follows:

- 1) Normal sodium TCP from a plant operation
- 2) Sodium TCP made from distilled triphenol
- 3) Sodium TCP made from trichlorophenol purified by the Diamond Alkali technique (dilution, filtration, precipitation and washing)

In this experiment acne was produced in the Halowax control cases and in the cases exposed to the normal plant produced sodium TCP; no acne developed in the cases exposed to the treated TCP samples in the concentrations used.

Dr. Suskind stated that the evolution of chlor-acne is very similar to Acne Vulgaris. Dr. Oettel and Dr. Suskind agreed that massive doses of Vitamin A₁ (100,000 units per day) are effective in Acne Vulgaris. Vitamin therapy was unsuccessful in the Monsanto cases. Dr. Oettel was of the opinion that treatment was too late and stated that they have found that massive doses given in the very early signs of chlor-acne have often resulted in complete clearing of symptoms in 2 to 3 weeks.

Dr. Suskind stated that there is evidence that people develop acne from inhalation or ingesting of Halowax and Dr. Oettel agreed that acne need not come from percutaneous absorption but also may be systemic in origin. Dr. Suskind stated that in the Monsanto cases the skin problem was not disabling but the many other symptoms such as vertigo, aching muscles,

CONFIDENTIAL
PROTECTIVE ORDER

C15584

dyspnea and headaches were. In close checking the varying secondary symptoms (once termed bizarre) it developed that all of the typical symptoms were common to both the German and Monsanto cases with the exception of dyspnea and intolerance to cold.

Dr. Oettel stated that materials such as Halowax and trichlorophenol are not in themselves acnogenic but that the offending contaminant is an "oxidate". Residues from the Badische decomposition have been extracted and elemental analyses made of the extracts (carbon, hydrogen, chlorine, oxygen). Following this, a series of oxygen bearing, chlorine bearing ring hydrocarbons were synthesized and checked for animal toxicity, using rabbits. Comparative acute toxicity of four of the compounds are as follows:

- 1) triphlorophenol - greater than 1 gram per kilogram
- 2) tetrachloro naphthalene - 50 mg per kilogram
- 3) tetrachloro diphenylene oxide - 0.1 mg per kilogram
- 4) tetrachloro diphenylene dioxide - 0.005 mg per kilogram

The latter compound (also called tetrachloro diphenyl dioxane) checks more closely by elemental analysis with the extract of the residues from the decomposition. Dr. Oettel is convinced that this is the active agent. They have developed a liver function test for rabbits which involves a micro determination of Bromsulphalein retention. This is used as a control test on purchased trichlorophenol (feeding 1 gram of the sample per kilogram of body weight to each of three rabbits). If there is no more than 5% of BSP retention in 5 days, the material is approved for processing. Dr. Oettel stated positively that there had been no cases of chlor-acne in the 245T synthesis operation.

CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER

C15585

In a later conversation while returning to St. Louis, it developed that the 1953 decomposition at Badische Works did not occur early in the hydrolysis as in the case of both Monsanto and Diamond Alkali, but was in the stripping of excess methanol following the hydrolysis when the batch was dehydrated and decomposed. The decomposition pressure was relieved through normal pressure relief devices and the autoclave was also left full of a mass of coke so hot that it was "gleaming". Badische has been able to reproduce the decomposition of NA-TCP by dehydration in the presence of iron. (This appears to still leave unexplained the type of decomposition experienced by Monsanto and Diamond Alkali.)

Badische no longer produces TCP but purchases trichloro-phenol from Bayer and uses the BSP test for acceptance or rejection of each lot. Bayer professes to have had no chlor-acne but Dr. Oettel doubts their veracity. Dr. Oettel stated that Boehringer in Ingelheim, Germany had a slight decomposition in sodium TCP production and have had many cases of chlor-acne for many years. Their trichloro-phenol gave high results (positive) by the BSP tests.

Dr. Oettel volunteered to run BSP tests for Monsanto on samples which we might forward to him. Mr. Weger agreed to have responsibility for following up on this work.

COPIES
SENT TO PROTECTIVE DIV.

C15586