

cc: noo. Dr. S. J. Green ✓

Research

SRE/AIW/3.5

18th April, 1973

FOR FILING

Dr. E. Karbe,
Battelle Institut, eV,
6 Frankfurt am Main 90,
Postfach 900160,
West Germany.

Dear Eberhard,

Following my visit to Frankfurt last week, I would confirm the main points of our discussions as follows -

General

You informed me that the proposal by Battelle Columbus on the storage and retrieval of data on cancer research had not been accepted by the NCI. No decision will be taken by the West German Government until 1974 regarding the proposal by Battelle, Frankfurt to examine the effect of inhaling lead alone and together with tobacco smoke.

Mouse-Skin Painting

(a) Long-Term Experiments

Steady progress is being made with the B9, B10 and B11 experiments. No special problems had been experienced. The possibility of starting the next long-term test (B12) in the autumn was discussed; I was unable to confirm that samples would be available to start the experiment in September. Referring to a recent letter from Carworth, Dr. Sacherer suggested that by October, clean mice should be available and that this could be an important factor in deciding when to start the next long-term experiment.

(b) Promotion Experiments

The results of the extended comparison of samples B9-1 and B9-6 coupled with dose level effects had been checked against histological findings. The detailed results were examined in terms of hyperplasia and neoplasia occurring in sebaceous gland cells compared with the incidence of these lesions in epidermal cells. The highest incidence in the former occurred in animals treated with the least active materials, ie. DMBA plus solvent and low levels of DMBA with B9-6 condensate. In discussing this finding, you suggested that, with the more active materials, the lesion had progressed so that the lesions in sebaceous gland cells were no longer noted.

100995407

Group
Experiment
and
Control

It was also apparent that the incidence of keratin granulomas was much lower in this experiment compared with previous promotion tests. The reason for this is not clear, but it may be due to the duration of the experiment. It appeared unlikely that it was due to increased experience in diagnosis or a change in the animals. I undertook to examine the possibility of having the results analysed statistically prior to the Battelle report being finalised.

The current promotion experiment is also proceeding satisfactorily. On receipt, the animals were found to have a respiratory infection, but no subsequent health problems had been found. Because of the initial infection and the possible risk to the B11 experiment, the animals were housed in the F1 building together with the few remaining animals in experiment B9 and those in B10. The start of the experiment was delayed by two days due to concern over the purity of the DNBA, despite the fact that fresh vials stored in a refrigerator were to be used. A new supply was obtained and the lag between pre-treatment and condensate painting was maintained at 9 days. Approximately 12 animals had minor lesions following DNBA treatment, but these were now healed. Battelle will submit four-weekly reports on the incidence of lesions when significant numbers occur.

(c) Statistical Analysis of Long-Term Skin-painting Experiments

The proposed improvements in the definition of tumour bearing animals (TBA) had been communicated to Battelle prior to my visit. The first improvement, ie. to consider in the detailed analysis only those animals which had a lesion (papilloma or "tumour") present at the week of death; had been agreed in correspondence with Dr. Königsmann. You also agreed that this improved definition should be incorporated.

Therefore, the discussion with you and Frau Weiss centred on the second proposed improvement, ie. whether TBA should be defined as those animals which had tumours confirmed by histology. You argued that when "no information" could be recorded concerning the character of the tumour (0 in Col. 54), this usually applied to an animal bearing a lesion at death, which was autolysed or cannibalised. Acceptance of the second definition would exclude a number of genuine TBAs. You put forward two main points as follows :

- (a) it has been found large lesions, ie. 4mm or greater in diameter, can be classified as neoplastic with about 99% certainty, and
- (b) whereas small lesions are seldom cannibalised; the incidence of cannibalism is higher with large lesions.

On this basis, you considered that it would not be reasonable to define TBA as those with histologically confirmed tumours.

At this stage, the discussion turned to the treatment to be used for the Battelle report on Experiment B2. I indicated that I had insisted that the statistical analysis of the experiment, which had already been sent to Battelle, should stand and that the revised definition should be used initially for the report on Experiment B3. You agreed to this proposal, but felt that the

100995408

FROM
20.11.1977
100995409

Battelle assessment of TBA excluding regressions (Chapter 8) should be modified. I considered that this could be confusing at some time in the future, and that the re-definition of TBA should take place simultaneously in the report on B3. You agreed with this argument, but in the discussion with Frau Weiss, it was stated that Dr. Königsmann extracted for Chapter 8 data on animals which had tumours characterised by histology.

In the absence of Dr. Königsmann, the position was discussed with Dr. Sacherer and yourself. Dr. Sacherer had noted the urgency of the problem and was able to confirm that Dr. Königsmann was also concerned that the second proposed definition (confirmed by histology) would exclude a number of genuine TBA from the analysis. I pointed out that there was obviously a delicate balance between excluding a small proportion of TBA from the analysis and, on the other hand, including a small number of TBA which had "tumours" not confirmed by histology.

The considered opinion was that the definition of "animals bearing tumours at death" should be adopted and I agreed that the analysis would proceed on this basis. Essentially, this means that, starting with experiment B3, the analysis will exclude those animals which do not have at least one lesion present at the week of death.

Inhalation Research

(a) Promotion Experiment

Dr. Köster had completed the histological assessment of all the laryngeal lesions and, where appropriate, other pathologies. Photographs of slides are being prepared to illustrate the classification of laryngeal lesions and a few additional checks are being undertaken with special stains. Although Dr. Köster will prepare the draft report, the final report will probably be delayed until you return from the USA in July. Certain aspects of the report and the tabulations were discussed with you and Dr. Köster.

(b) Second Promotion Experiment

The design had been discussed during previous visits and I asked when it would be possible to start the experiment. Additional animal accommodation is available already and a third Hamburg Type II inhalation machine has also been installed. You agreed that facilities would be available in September and possibly in August; an additional technician would have to be engaged and/or trained for the smoke exposure/animal handling.

(c) Vitamin A Experiment

You were pleased with the quality of the hamsters received from Roberts of Basingstoke. The young animals were acclimatised to one round of smoke in 9 days; the double exposure group were maintained at that level for one week after which the dose was increased by 1 puff per day. The higher dose level groups had

100995409

-5-

Please pass on my kind regards and thanks for your excellent hospitality to all concerned.

Yours sincerely,



S. R. EVELYN

cc: Dr. F. A. Sacherer *FA*
Battelle, London

100995411