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B R O W N H.T.

TOXICOLOGICAL ASSESSMENT WITH

SPECIAL REFERENCE TO

PIGMENT DEPOSITION

IN

MESENTERIC LYMPH NODES AND KIDNEYS

AUTHOR

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1. INTRODUCTION

- 1.1 I have been asked by the E.E.C. Colours Group, in response to a request from the S.C.F., to assess the toxicological significance of the results of four recent studies carried out by B.I.B.R.A. with special reference to pigment deposition in the mesenteric lymph nodes and kidneys. The four studies were commissioned by the E.E.C. Colours Group in response to specific requests by the S.C.F. and U.K. regulatory authorities.
- 1.2 The four studies are as follows:-
 - 1.2.1 B.I.B.R.A. Report No. 1/1981: The metabolic disposition of ^{14}C -labelled Brown HT in the rat, mouse and guinea pig (May, 1981)
 - 1.2.2 B.I.B.R.A. Report No. 1/189/78: Report of a teratology and embryo toxicity study with Chocolate Brown HT in the rat (October, 1978)
 - 1.2.3 B.I.B.R.A. Report No. 278/2/81: The absorption, tissue distribution and excretion in the rat of Brown HT following single oral and subacute oral treatment (May, 1982)
 - 1.2.4 B.I.B.R.A. Report No. 294/1/81: Multigeneration toxicity study with Brown HT in rats in 7 volumes (March, 1982)
- 1.3 In the context of my investigation and assessment these studies needed to be considered in the light of the results of five other studies, three of which have been published:-
 - 1.3.1 Hall, E.E., Lee, F.S. and Fairweather, F.A. (1966) Acute (Mouse and Rat) and short-term (Rat) toxicity studies on Chocolate Brown HT. Fd. Cosmet. Toxicol., 4, 143.

- 1.3.2 Chambers, P.L., Hunter, C.G. and Stevenson, D.E. (1966) Short-term study of Chocolate Brown HT in rats. Fd. Cosmet. Toxicol., 4, 151.
- 1.3.3 Hendy, R.J., Butterworth, K.R., Gaunt, I.F., Hooson, J. and Grasso, P. (1975) Short-term toxicity study of Brown HT in pigs. B.I.B.R.A. Research Report No. 17/1975.
- 1.3.4 Carpanini, F.M.B., Butterworth, K.R., Gaunt, I.F., Kiss, I.S., Grasso, P. and Gangolli, S.D. (1975) Long-term toxicity studies of Brown HT in rats. B.I.B.R.A. Research Report No. 19/1975 .
- 1.3.5 Drake, J.J-P., Butterworth, K.R., Gaunt, I.F. and Hardy, J. (1978) Long-term toxicity studies of Brown HT in mice. Toxicology, 10, 17.

2. CONSIDERATION OF STUDIES

- 2.1 I considered the reports and data from all these studies with special reference to pigment deposition in tissues and to pathological changes that might be secondary to pigment deposition.
- 2.2 As it is my understanding that these reports have already been considered and evaluated by the S.C.F., I have relegated my review of the studies to an Appendix.
- 2.3 In the light of all these reports it seemed unlikely to me that any re-examination of the histopathological material from the many studies conducted at B.I.B.R.A. would lead me to a conclusion that was substantially different from that expressed in their multigeneration study, viz. that 250 mg/kg/d Brown HT is a no untoward effect level in the rat.

3. RESULTS OF REVIEW OF HISTOPATHOLOGICAL MATERIAL FROM F₃-GENERATION RATS OF THE MULTIGENERATION STUDY

- 3.1 On 27.6.83 I visited the B.I.B.R.A. Laboratories to review the histopathological material from the F₃ generation rats in the studies. Available for me were the thousands of sections from the study carefully arranged in histology number order. In the time available to me, I decided that I could do no more than review sections as follows:-
- 3.2 Sections of thyroid, liver, kidney, heart, voluntary muscle, caecum, thymus, mesenteric lymph node and cervical lymph node from:-

2 male controls	:	Animal Nos. 1 and 2
5 top dose males	:	" " 255,258,263,264 & 26
2 female controls	:	" " 326 and 327
5 top dose females	:	" " 604,606,607,608 & 60

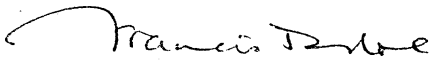
3.3 Sections of mesenteric lymph node only from:-

10 top dose males : Animal Nos. 271,272,273,279,
280,281,285,288,
289 and 291

5 top dose females: " " 614,615,620,621
and 626

4. Adequate sections of all the above tissues were available except that I could not find any section of the thyroid of control female rat No. 327 or any section of the cervical lymph node of high dose female rat No. 607.
5. None of the tissues that I examined exhibited any evidence of departure from a status which I would regard as normal for young rats. The thymuses showed no evidence of involution and the lymphoid tissue of the mesenteric and cervical lymph nodes of both treated and control rats exhibited the level of proliferative activity to be expected in young rats.
6. Despite careful search and the use of high powered magnification, I could find no evidence of pigment deposition in any of the tissues I examined. Specifically, there was no pigment deposition in the follicular cells of the thyroid. The Kuppfer cells of the liver, like the parenchymal cells of that organ, were wholly free of pigment. I could find no evidence of pigment deposition in the proximal convoluted tubules or at any other site in the kidney. Nor was there any evidence of pigment deposition in cardiac or voluntary muscle or in the wall of the caecum. Finally, in the mesenteric lymph nodes, I could see no pigment-laden macrophages in the sinuses and no other evidence of pigment deposition.
7. My examination of the kidneys provided no explanation of the higher kidney weight seen in high dose rats compared with controls (~~see table above~~). Also I saw no evidence of pelvic nephrocalcinosis or of any other form of nephrocalcinosis in any rat.
8. Opinion based on material examined

On the basis of my examination of a small, but in my view, representative and adequate sample of the histopathological material from the multigeneration study, it is my view that exposure over 3 generations to 250 mg/kg Brown HT gave rise to no accumulation of pigment in a form that survived normal tissue processing in the tissues that I examined. More importantly, it is clear to me that treatment gave rise to no histopathological change in any of the tissues I examined. In particular, my careful examination of the mesenteric nodes revealed no means by which I could distinguish between treated and control rats and no evidence of stimulation or of atrophy of lymphoid tissue. Finally, I detected no effect of treatment on the histopathological appearances of the kidney.


Signed: Francis J.C. Roe
DM, DSc., FRC Path.
28th June 1983