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SCIENTIFIC DATA REVIEWS
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 4 1986

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Baygon

FROM: Esther Rinde, Ph.D. E. Rinde 8/21/86
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

TO: J.S. Ellenberger
Product Manager #12
Special Review Branch
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on June 26, 1986 to discuss and evaluate the data base on Baygon, with particular reference to its oncogenic potential in SPF rats and mice.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated).

William L. Burnam

Bertram Litt

Diane Beal

Judith Hauswirth

John A. Quest

Esther Rinde

2. Reviewers: (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Byron Backus (Reviewer)

Marcia Van Gemert (Section Head)

3. Peer review members in absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Theodore M. Farber	Theodore M. Farber
Richard Hill	Did not read
Stephen Johnson	
Anne Barton	
Reto Engler	
Louis Kasza	
Robert Beliles	Robert P Beliles

B. Material Reviewed:

The material available for review consisted of the following:

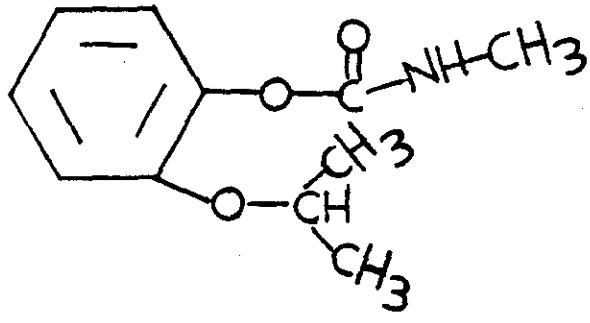
A. DER: Review of a two-year SPF ($CF_1/W74$) Mouse Oncogenicity and Teratogenicity Study of Baygon. Mobay. (Memorandum from R. Zendzian, 6/21/82)

B. DER: Baygon Oncogenicity - 2 year feeding study in SPF (BOR:WISW) Rats. Mobay. (Memorandum from B. Backus, 1/18/85)

C. DERS: Baygon Mutagenicity and Metabolite Studies. (Memorandum from B. Backus, 1/18/85)

C. Background Information:

Baygon, also known as propoxur (2-isopropoxy-phenyl-N-methylcarbamate) is a carbamate insecticide, widely used in PCO (pest control operator) products, household sprays, pest strips, and in several flea control pet products (sprays, dust and collars). No tolerances have been issued.



BAYGON

D. Evaluation of Oncogenicity Evidence for Baygon:

1. Two-Year feeding study in SPF Mice (CF_1/W74 from breeder Winkelmann, Borchen) - Bayer Report No. 9954

Technical Baygon (99.6%[1]) was fed in the diet to 60 male and 60 female SPF mice at concentrations of 0, 700, 2000 and 6000 ppm for 24 months.

The EPA reviewer concluded that the study showed no evidence of oncogenicity in mice at doses up to 6000 ppm (1191 mg/kg/d (males) and 1374 mg/kg/d (females); however it was noted that there was a discrepancy between the doses used and the acute oral toxicity of the compound [B. Zendzian Memo 6/21/82].

The Committee expressed some concern as to the validity of this study and whether it was a true negative, based on the reviewers concerns, regarding the LD_{50}.

The above concern was based on the LD_{50}[1] of technical Baygon, by intubation in rats, however there are no LD_{50} data for the mouse; furthermore, the toxicity of a food preparation, given over a period of a day (instead of at one time, via intubation) may not be equivalent.

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[1] Starting with week 7, a 90% concentration in Wessalon S was used.

[2] Baygon is a carbamate cholinesterase inhibitor and its reported LD_{50} in rats is about 100 mg/kg (by oral intubation of a technical aqueous preparation).

[3] "Stability data showed 94-99% nominal (concentration) at day zero, with a 14-36% loss over the two week period following mixing" [Zendzian review 12/23/85].

2. Two-year feeding study in SPF Rats - BOR:WISW (SPF Cpb) from breeder Winkelmann, Borchen.

Baygon (99.4% a.i.) was fed in the diet to 60 male and 60 female SPF rats at concentrations of 0, 200, 1000 and 5000[1] ppm for 106 weeks. The incidence of tumors was as shown in Table I and II (pgs. 6 & 7).

At 1000 and 5000 ppm there was an increased incidence of both papillomas and carcinomas of the bladder. At 5000 ppm:

°The incidence of carcinomas alone was statistically significant at the interim (1-year) sacrifice for both males and females, and for males only in animals surviving to terminal sacrifice.

°The incidence of papillomas alone, at the high dose, was highly statistically significant in both sexes at both interim and terminal sacrifice.

°The combined incidence (papillomas and carcinomas) at the high dose for both sexes, at both interim and terminal sacrifice was highly significant ($p<<.0001$).

The committee noted the unusually high incidence (67-75% papillomas and carcinomas combined at the high dose; 0% in controls) of bladder tumors (a rare tumor type) and that they were not accompanied with crystalline deposits as is often the case with many other chemicals which produce bladder tumors. The dose-response seen at the mid and high dose for hyperplasia and its early onset (1-year) were also thought to be of significance.

In addition, there was an increase, of borderline statistical significance ($p < .055$) in the incidence of carcinoma of the uterus, associated with early dose-related deaths with this tumor, in female rats. In the high-dose female rats, there was a definite tendency for this tumor to develop earlier and/or grow more rapidly[2]

Testing was conducted at high enough doses in this study as evidenced by neuropathy of the sciatic nerve and muscular atrophy observed in animals at the 5000 ppm level (MTD was exceeded). There were also lower body weights (statistically significant) at 5000 ppm in both sexes.

It was noted that in a previously submitted 2-year feeding study in rats, there were apparently no indications of bladder effects at dietary levels of 250, 750, 2000 or 6000 ppm Baygon. However, pathology reports were reported for only five rats per sex per group (in addition to reports of palpated tumors). Considering the high incidence of bladder hyperplasia in the more recent study (almost 100%), some questions were raised about this earlier one. Data for the latter were not available to compare conditions of the two studies (i.e. rat strains used, et al.)

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[1] The calculated dose equivalent to 5000 ppm (for the rat) is 111 mg/kg/d, which approximates the LD_{50}, however the toxicity of a food preparation, given over a period of a day (instead of at one time, via intubation) may not be equivalent.

2 Compared to controls (and lower-dose groups).

TABLE I

INCIDENCES OF Epithelial HYPERPLASIA, PAPILLOMA AND CARCINOMA OF THE BLADDER AT THE INTERIM (1-YEAR) SACRIFICE:

Bladder Epithelial	GROUP I 0 ppm M	GROUP I 0 ppm F	GROUP II 200 ppm M	GROUP II 200 ppm F	GROUP III 1000 ppm M	GROUP III 1000 ppm F	GROUP IV 5000 ppm M	GROUP IV 5000 ppm F
Hyperplasia	0/10	0/10	0/10	0/10	4/10	1/10	10/10	10/10
Papilloma	0/10	0/10	0/10	0/10	0/10	0/10	2/10	0/10

INCIDENCES OF UROTHELIAL HYPERPLASIA, PAPILLOMA AND CARCINOMA OF THE BLADDER IN ANIMALS STILL ALIVE AFTER THE INTERIM SACRIFICE:

Bladder Epithelial	GROUP I 0 ppm M	GROUP I 0 ppm F	GROUP II 200 ppm M	GROUP II 200 ppm F	GROUP III 1000 ppm M	GROUP III 1000 ppm F	GROUP IV 5000 ppm M	GROUP IV 5000 ppm F
Hyperplasia	1/48	0/48	1/50	0/48	9/49	4/47	42/47	48/48
Papilloma	0/48	0/48	0/50	0/48	1/49	0/47	25/47*	28/48**
Carcinoma	0/48	0/48	0/50	0/48	0/49	0/47	7/47†	5/48
Papilloma or carcinoma	0/48	0/48	0/50	0/48	1/49	0/47	32/47 (68%)	33/48** (69%)

*Does not include equivocal neoplasm for animal #418

**Does not include equivocal finding for animal #459

†Does not include possible early carcinoma finding for animal #412

INCIDENCES OF UROTHELIAL HYPERPLASIA, PAPILLOMA AND CARCINOMA OF THE BLADDER IN ANIMALS SURVIVING TO TERMINAL (106-WEEK) SACRIFICE

Bladder Epithelial	GROUP I 0 ppm M	GROUP I 0 ppm F	GROUP II 200 ppm M	GROUP II 200 ppm F	GROUP III 1000 ppm M	GROUP III 1000 ppm F	GROUP IV 5000 ppm M	GROUP IV 5000 ppm F
Hyperplasia	1/37	0/38	1/44	0/40	8/41	3/40	36/36	36/36
Papilloma	0/37	0/38	0/44	0/40	1/41	0/40	22/36*	21/36**
Carcinoma	0/37	0/38	0/44	0/40	0/41	0/40	5/36†	3/36
Papilloma or carcinoma	0/37	0/38	0/44	0/40	0/40	1/41	27/36* (75%)	24/36 (67%)

*Does not include equivocal neoplasm for animal #418

†Does not include possible early carcinoma finding for animal #412

**Does not include equivocal finding for animal #459

TABLE II

INCIDENCES[1] OF CARCINOMA OF THE UTERUS

GROUP I 0 ppm	GROUP II 200 ppm	GROUP III 1000 ppm	GROUP IV 5000 ppm
3/48	4/48	3/47	8/48

[1]Overall incidence - includes animals terminally sacrificed.

3. Historical Control Information

No information was submitted by the registrant at this time. Historical Control data for this strain of rat have been requested from the registrant.

E. Additional Toxicology Data on Baygon:

1. Metabolism:

Baygon can undergo a number of rapid metabolic reactions in vivo , including depropylation, hydroxylation of the N-methyl group, hydrolysis, ring hydroxylation and cleavage of the carbamate group (Figure 1).

2. Non-Oncogenic Toxicological Effects

The oral (by intubation) LD_{50} in the rat for technical Baygon is usually reported at about 100 mg/kg, with some variation above and below this value.

When formulations are tested, however, the LD_{50} in the rat can range from < 1 gm/kg to > 5 gm/kg. Reported oral LD_{50} values:

- for a product containing 8% Baygon = 884 mg/kg for males and 548 mg/kg for females.
- for a product containing 10% Baygon = 3 gm/kg for males and 2 gm/kg for females.
- for a product containing 2-3% Baygon = > 5 gm/kg.

Dermal LD_{50} of Baygon in the rat was reported as > 1 gm/kg (technical Baygon) and > 4 gm/kg (45% formulation).

* * * *

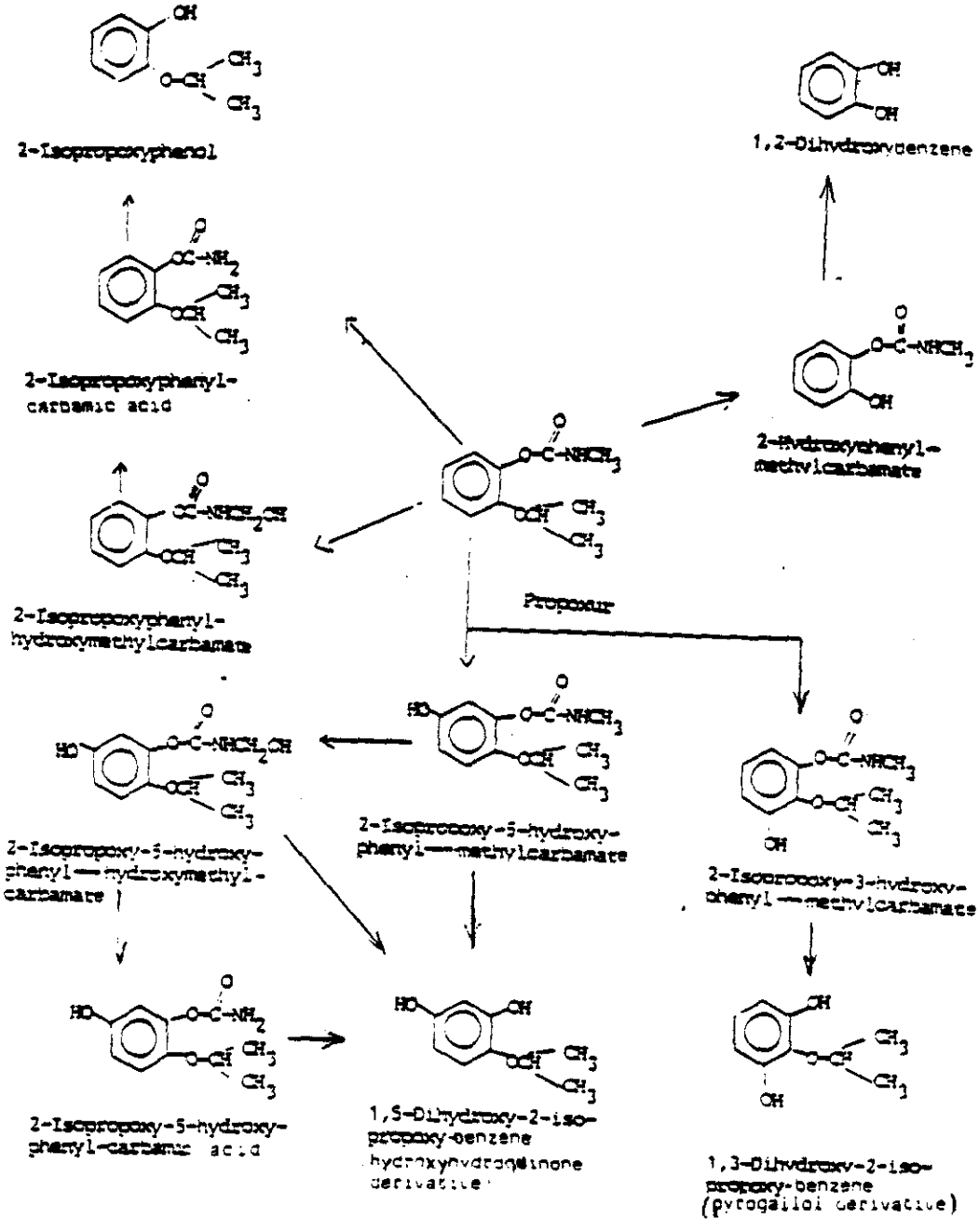
Rabbits dosed with Baygon by oral intubation (of a suspension in 0.5% "cremophor" in water) up to 10 mg/kg/d (days 6 - 18 of pregnancy) did not demonstrate any teratogenic or fetotoxic effects. It was noted, however, that since no toxic or pharmacologic effects occurred in the dams at any dose, the doses used in this study may not have been high enough [Zendzian 6/8/82].

In a rat teratology study (by feeding, during entire period of gestation - only 10 females/dose level) both maternal and fetal toxicity were noted at 3000 ppm (150 mg/kg/d). The NOEL for maternal and fetal toxicity was 1000 ppm and there was no evidence of teratogenic effects at 10,000 ppm (HDT).

In the 2-year rat feeding study (for oncogenicity), increases in the incidence and/or degree of both neuropathy of the sciatic nerve, and muscular atrophy were noted in the animals dosed at 5000 ppm (HDT).

Figure 1

As part of the submission entitled "Toxicology Studies on Propoxur and its metabolites" the following diagram was included in the material received from Mobay 10/23/84 (in Acc. 255177) indicating some of the compounds found in rat urine following administration of Baygon:



According to information in the one-liners, O-isopropoxyphenol has been identified as being present in urine samples of human volunteers who were orally dosed with 50 mg of Baygon.

3. Mutagenicity:

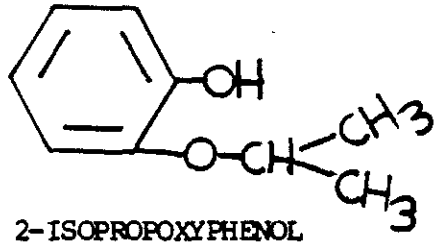
In Ames Assay, Baygon (98%) did not show detectable mutagenic activity with or without activation.

In a rec⁻ assay with Bacillus subtilis N1G45 (rec⁻) and N1G17 (rec⁺) there was no evidence of mutagenicity at 3, 30 or 300 ug technical (98%) Baygon/disc.

Although the above studies were reviewed and accepted by a Toxicology Branch reviewer in the past, by current standards, both assays would be classified as unacceptable. (It is questioned whether Baygon was tested at a high enough dose level in both assays; and there is no indication that the rec⁻ assay was run with S9) [B. Backus 6/30 and 8/14/86].

In the mouse dominant lethal assay, a single dose of 10 mg/kg of technical (99.2%) Baygon showed no effect on reproduction.

As part of the information EPA received 10/23/84 from Mobay, there were a number of mutagenicity studies on Baygon and some of its metabolites. All tested negative for mutagenicity, including 2-isopropoxyphenol, a metabolite found in both rat and human urine.



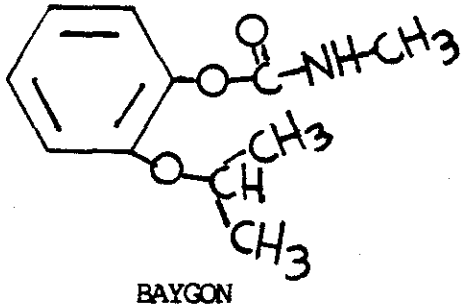
2-ISOPROPOXYPHENOL

The committee concluded that adequate mutagenicity studies were not available and that the registrant should be asked to provide a complete battery of mutagenicity tests. Some concern was also expressed that some of the mutagenicity tests may not be sensitive to this class of chemicals.

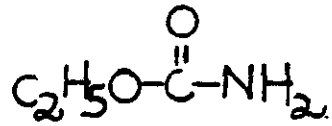
As noted in the next section, Baygon has some structural similarity to Urethane, which is generally negative in the Ames Assay.

4. Structure-Activity Correlations

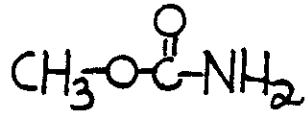
Baygon has some structural similarity to Urethane, a known oncogen:



BAYGON



URETHANE
(Ethyl Carbamate)



METHYL CARBAMATE

Urethane is carcinogenic in rats and mice and (various other species) by a number of routes, giving rise to (among others) lung and liver tumors [IARC - Vol. 7]. A structural analog of urethane, methyl carbamate, has been found to produce liver tumors (only) in both sexes of Fisher rats, but not in mice. It was noted, however, that the substituted aromatic structure of Baygon may have different activity from that of the aliphatic ethyl or methyl carbamate.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding toxicology data on Baygon to be of importance in a weight of evidence determination of oncogenic potential.

1. Administration of Baygon in the diet to SPF rats is associated with:

In The Bladder

- A statistically significant increase over the control in the incidence of papillomas, and of carcinomas, in both male and female rats at the high dose (in the absence of crystalline deposits in the bladder) at the interim (1-year) sacrifice.
- A highly statistically significant increase in the combined overall incidence of papillomas and carcinomas at the high dose, in both males and females (67-75% vs 0% in the control).

  (Bladder tumors in the rat are relatively rare and have a low background incidence [L. Kasza][1].)
- A dramatic and statistically significant, dose-related increase in bladder epithelial hyperplasia at the mid and high dose, with 100% incidence at the high dose in animals surviving to terminal sacrifice.
- Earlier onset of bladder epithelial hyperplasia (at the interim - 1 year sacrifice).

and

In The Uterus

- An increased incidence of carcinoma associated with early dose-related deaths.
- Earlier onset of uterine carcinoma at the highest dose tested (5000 ppm).

2. Urethane and methyl carbamate have some structural similarity to Baygon. Urethane causes increases in lung and liver tumors (et al.) in rats and mice. Methyl carbamate produces liver tumors in both sexes of male and female Fisher rats (but not in mice).

3. In the SPF mouse, Baygon did not show evidence of oncogenicity.

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1 This information was not available at the time of the Peer Review Meeting.

G. Classification of Oncogenic Potential:

Criteria contained in the proposed EPA Guidelines [Draft Jan.7, 1986] for classifying a carcinogen were considered:

For Group C - Possible Human Carcinogen:

"Limited evidence of carcinogenicity .... means that the data suggest a carcinogenic effect but are limited because:

a) The studies involve a single species, strain, or experiment and do not meet the criteria for sufficient (see Group B, part c);
b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or
c) an increase in the incidence of benign tumors only."

For Group B - Probable Human Carcinogen:

"Sufficient evidence of carcinogenicity .... indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors:

a) in multiple species or strains; or
b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or
c) to an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age of onset.

Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure."

The Committee agreed that the available evidence for Baygon provided limited evidence of carcinogenicity in animals, based on positive findings in both sexes of SPF rats in an acceptable 2-year feeding study, which satisfies Part a) of the criteria for Group C: "The studies involve a single species, strain, or experiment and do not meet the criteria for Group B, Part C.

Classification of Baygon in the higher B-2 category was also considered, based on the unusually high incidence of bladder tumors in the rat study, the early onset of hyperplasia and the somewhat uncommon finding of bladder tumors in the absence of crystalline deposits. It was agreed that while these factors are suggestive of a higher classification, the evidence at this time is not sufficient for a B-2 classification. The relative rarity of the tumor type (bladder) was also discussed, but could not be confirmed at the time of the meeting.

Based on the above information, the Peer Review Committee members attending on 6/26/86 concluded that Baygon should be classified as Category C, "Possible Human Carcinogen", and that a quantitative estimation of the oncogenic potential for humans should be developed. [SEE NEXT PAGE (13)].

CONTINUED

G. Classification of Oncogenic Potential (contd.):

Subsequent to the Peer Review Meeting for Baygon on 6/26/86, some members of the Committee, who were unable to attend at that time, requested that the classification of Baygon be reconsidered. The following new information has now been considered by the Committee: 1) the relative rarity of the tumor type has been confirmed and 2) the apparent discrepancy of the dosage levels in the mouse may be related to differences in route of administration and species differences (see page 4).

* * * *

Reviewing the evidence:

* Neoplasias in only 1 species (rat), but with
* Unusually high incidence of bladder neoplasias (67-75% in both sexes at the high dose vs 0% in controls)
* Relative rarity of the tumor type (bladder)
* Early onset of hyperplasia and papilloma of the bladder,and the
* Somewhat uncommon finding of bladder tumors in the absence of crystalline deposits.

Based on the above evidence, all three criteria for Part c) of Category B of the Guidelines are met, ie:

c)to an unusual degree in a single experiment with regard to high incidence [MET], unusual site or type of tumor [MET], or early age at onset [MET]... .

This re-evaluation of the classification of Baygon was sent to all Committee members for comment. No dissenting comments were received - and Baygon has been re-classified as a Category B_2: "Probable Human Carcinogen".

H. Additional Data Required

The adequacy of the mouse study (which appears to be negative) was also considered and whether the registrant should be asked to repeat the study was discussed. It was decided that a new mouse study would not be requested at this time, however as part of the Registration Standard for Baygon, clarification as to protocol used and results obtained should be investigated.

The Committee recommended that the registrant be asked to provide a complete battery of mutagenicity tests.

G. Classification of Oncogenic Potential (contd.):

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Chemical: ~~o-Isopropoxyphenyl methylcarbamate~~

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HED File Code 21200 PEER REVIEW
Memo Date: 09/04/86 12:00:00 AM
File ID: 00000000
Accession Number: 000-00-0049

HED Records Reference Center
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