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Control No CBI

EXXON COMPANY, U.S.A.

POST OFFICE BOX 2180 • HOUSTON, TEXAS 77252-2180

May 18, 1993

Re: Wax - Rat Feeding Study

HEALTH SERVICES DEPARTMENT

KENNETH G. GOULD, JR., M.D., Ph.D.
MEDICAL DIRECTOR

**Document Control Officer
Chemical Information Division
Office of Toxic Substances
Environmental Protection Agency
401 M Street S.W.
Washington, D. C. 20460**



INIT 06/08/93



88930000319

08 JUN 1993 11:00

Dear Document Control Officer:

On August 14, 1992, Exxon Company, U. S. A. filed a Toxic Substance Control Act 8(e) notification based upon a toxicology study initiated and sponsored by CONCAWE (The Oil Company's European Organization for Environmental and Health Protection). The toxicology study was a 90-day feeding study in Fischer 344 rats and was conducted at the laboratories of BIBRA Toxicology International, Surrey, Great Britain. Male and female Fischer 344 rats were fed a diet mixed with various doses of food grade mineral hydrocarbons, one of which has been defined as "Low Melting Point Wax" (low melt point paraffin wax with no CAS number defined). The notification focused on inflammatory lesions in the mitral valve of the heart in the high dose groups and other biological findings (granulomatous-type formations in the liver and histiocytosis in the mesenteric lymph nodes. .

Exxon Company, U. S. A. is now submitting a supplemental notification to the August 14, 1992 TSCA 8(e) substantial notification based upon additional studies. These studies were also 90-day rat feeding studies, conducted at the laboratories of BIBRA Toxicology International but reported by the European Wax Federation (Heerhugowaard, The Netherlands). The report indicated that Fischer rats were fed three wax materials; a micro/paraffin wax mixture (MP), and a high melting intermediate paraffin wax (P-64), each at dose levels of 0.02, 0.2, and 2.0% wax, and Low Melting Point (LMP) at a single dose level of 2.0%. The rats fed at a 2.0% dose level of wax (MP, P-64, & LMP), displayed focal inflammatory lesions of the mitral valve of the heart. This effect was still observed following the 90-day reversal period. Other histopathologic findings were also found including microgranuloma/granuloma formations in the liver and histiocytosis in the mesenteric lymph nodes. These were essentially the same results as reported in our August 14, 1992 notification. An Exxon summary of these preliminary findings is attached.

Exxon Company U. S. A. is a domestic refiner of hydrotreated paraffin wax, which shares similar physical/chemical properties to the tested materials.

If you require additional information, feel free to call Stephen E. Killiany, Jr. (713-656-3904).

KGG/SEK
Attachment
waxhmi.doc



19 pgs

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EXXON COMPANY, U. S. A. SUMMARY
HISTOPATHOLOGIC FINDINGS FROM A 90-DAY FEEDING STUDY
OF A HIGH MELTING INTERMEDIATE PARAFFIN WAX, A MICRO/PARAFFIN WAX MIXTURE AND
A LOW MELTING POINT WAX IN FISCHER 344 RATS

MAY 6, 1993

Exxon Biomedical Sciences, Inc. received a draft report of the European Wax Federation (Heerhugoward, The Netherlands) 90-day toxicity study of a high melting intermediate paraffin wax alternatively identified as paraffin wax 64 (P-64), a micro/paraffin wax mixture (MP), and a low melting point wax (LMP). The micro/paraffin wax mixture was a 50:50 blend of LMP and a high melting point microcrystalline wax. The study, conducted at the laboratories of BIBRA Toxicology International, Surrey, Great Britain, was a comprehensive 90-day toxicity study in Fischer 344 rats. Exposure was via the feed. Paraffin wax 64 and MP were tested at dose levels of 0.02%, 0.2% and 2.0%. LMP, which has been previously tested, was tested at the 2.0% dose level only. After 90 days, groups of rats exposed to the 2.0% dietary level were placed on control diet for an additional 90-days to evaluate the potential for recovery from exposure.

The report indicated that female Fischer rats fed three wax materials (LMP, MP, and P-64) at a 2.0% dietary level displayed focal inflammatory lesions of the mitral valve of the heart. This effect was still observed following the 90-day reversal period. Male rats fed the 2.0% dose of MP and LMP wax exhibited the same focal inflammatory lesions of the mitral valve of the heart. However, no effect was observed in the mitral valves from the male rats fed 2.0% P-64. Curiously, this same treatment group (male rats fed 2% P-64 wax), which was allowed to recover during a 90 day reversal period, did have a few animals displaying the mitral valve lesions. The same mitral valve effect was also observed in the male rats fed the 2.0% dose of MP and LMP wax following the 90-day reversal period. The focal inflammatory lesion of the mitral valve of the heart was characterized as "a thickening of the mitral valve and a focal chronic inflammatory cell infiltrate".

Other histopathologic findings were also found in rats fed the three wax materials. In general, these findings included microgranuloma/granuloma formation in the liver at the 0.2% and 2.0% feedings levels and histiocytosis in the mesenteric lymph nodes at all dose levels. The cervical lymph nodes of rats fed the three wax materials at 2.0% were also examined and found to exhibit histiocytosis. These results were statistically significant in the rats fed LMP and the MP mixture (both sexes), and P-64 (female only). This finding was markedly reduced following the recovery phase.

Biological findings similar to those reported above have been previously reported to the Administrator by Exxon in a TSCA 8 (e) notification letter dated August 14, 1992. Similar pathology results in the mitral valve of the heart were found in both male and female Fischer rats fed a diet of 2.0% (male and female) and 0.2% (female only) LMP wax. This study also showed granulomatous-type formations in the liver and histiocytosis in the mesenteric lymph nodes of both males and females fed doses of 2.0% and 0.2% LMP wax. This study was also conducted by BIBRA International, however the sponsor was CONCAWE (The Oil Companies European Organization for Environment and Health Protection).

The effects in the mitral valve have only been observed in a single strain of rat and the significance of all these findings to humans remains unclear and is subject to further investigation.

RWB/JJF/SEK:ccr
Attachment (BIBRA Report)
waxhmi

0 0 0 3

DRAFT

**A 90-day feeding study in the rat with
two mineral waxes identified as
paraffin wax 64 (OFH-064) and
micro,paraffin wax mixture**

BIBRA Project No. 3.1205

58 JUN 10 11:11:58

STUDY TITLE

A 90-day feeding study in the rat with two mineral waxes
identified as paraffin wax 64 (OFH-64) and micro/paraffin wax mixture

AUTHORS

P.G. Brantom and J.K. Coatsworth

STUDY COMPLETED ON

PERFORMING LABORATORY

BIBRA Toxicology International
Woodmansterne Road
Carshalton
Surrey
SM5 4DS UK

SPONSOR

European Wax Federation
PO Box 86
1700 AB Heerhugowaard
The Netherland

LABORATORY PROJECT IDENTITY

Project No. 3.1205

Report No. 1205/1/93

GOOD LABORATORY PRACTICE

Acceptance of Report

I hereby declare that, to the best of my knowledge and belief, the study described in this report was conducted in compliance with accepted international standards of Good Laboratory Practice, and specifically, to US FDA Regulations for Non-Clinical Laboratory Studies as published in 43FR 59986, 22nd December 1978, and subsequent revisions.

Study Director:
P.G. Brantom, BSc, PhD, MIBiol, MCIM.

Signature.....Date.....

This report is approved by BIBRA Management as an accurate reflection of the study conducted.

Head of Customer and Information Services Division
P.G. Brantom, BSc, PhD, MIBiol, MCIM.

Signature.....Date.....

Director:
S.E. Jagers, BSc, PhD, MIBiol.

Signature.....Date.....

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Table 40. Histological findings in male rats on the main study fed either control diet, paraffin wax 64 at levels of 0.02%, 0.2% or 2.0%, micro/paraffin wax mixture at levels of 0.02%, 0.2% or 2.0% or low melting point wax at a level of 2.0%

The individual findings are shown in Appendix 36.

(* = $p \leq 0.05$; ** = $p \leq 0.01$; *** $p \leq 0.001$)

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-1205		FATES: ALL							
DAYS: ALL		SEX: MALE							
GROUP:		Control	64 0.02X	64 0.2X	64 2X	MP 0.02X	MP 0.2X	MP 2X	MP 2X
GROUP OF ANIMALS:		20	20	20	20	20	20	20	20
HEART/VENTRAL VALVE		#	#	#	#	#	#	#	#
# Ex	5	0	0	0	5	0	0	5	5
Valve birefringence -frozen	0	0	0	0	0	0	0	5	5
Valve inflammation -MIE	0	0	0	0	0	0	0	5	5
LIVER		# Ex	20	20	20	20	20	20	20
Vegetation, centrilobular	0	2	0	10	0	2	20	19	
Vegetation, peri-portal	0	0	1	0	0	0	0	0	
Calcified artery	1	0	0	0	0	0	0	0	
ICH Occasional/multiple	20	17	19	17	18	20	20	19	
Foci inflammatory cells	20	20	20	19	20	20	20	20	
Mixed granuloma, few	0	0	8	18	1	8	14	11	
Mixed granuloma, many	0	0	0	0	0	0	5	9	
Granuloma, few	0	0	0	0	0	0	4	4	
Granuloma, many	0	0	0	0	0	0	1	2	
MP INDEX-CERVICAL		# Ex	20	20	20	20	20	19	19
Neutrophils, minimal	0	0	1	2	0	4	7	8	
Neutrophils, mild	0	0	0	0	0	0	8	8	
Neutrophils, moderate	0	0	0	0	0	0	1	0	
MP INDEX-HEPATIC		# Ex	20	20	20	20	20	20	20
Neutrophils, minimal	1	8	2	0	10	3	0	0	
Neutrophils, mild	0	9	8	10	3	6	0	0	
Neutrophils, moderate	0	3	10	9	0	9	7	1	
Neutrophils, marked	0	0	0	1	0	2	13	19	
Ignited macrophages	3	0	0	0	0	0	0	0	
Granuloma, focal mild	0	0	0	1	0	0	0	0	

DRAFT

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-1205
DAYS : ALL

FATES: ALL
SEX: MALE

GROUP:	Control	64 0.02%	64 0.2%	64 2%	MP 0.02%	MP 0.2%	MP 2%	LMP 2%
NUMBER OF ANIMALS:	20	20	20	20	20	20	20	20
OTHER TISSUES AND LESIONS:	#	#	#	#	#	#	#	#
ES-few atrophic tubule	0	0	0	0	1	0	0	0
STOMACH-keratin cyst	0	0	0	0	0	1	0	0
ADRENALS-	0	0	0	0	0	0	1	0
EPIDIDYMIS-necrotic fat	0	0	0	0	0	0	1	0
TESTES-bilateral atropy	0	1	0	0	0	0	0	0

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Table 41. Histological findings in male rats on the reversal study fed either control diet, paraffin wax 64 at a level of 2.0%, micro/paraffin wax mixture at a level of 2.0% or low melting point wax at a level of 2.0%

The individual findings are shown in Appendix 37.

(* = $p \leq 0.05$; ** = $p \leq 0.01$; *** $p \leq 0.001$)

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-12051		AGES: ALL			
DAYS : ALL		SEX: MALE			
GROUP:		Control	64 ZX	MP ZX	LMP ZX
NUMBER OF ANIMALS:		10	10	10	10
HEART	# Ex	#	#	#	#
Focal myocarditis	3	4	1	5	
Valve inflammation -H&E	0	2	4*	5**	
Valve birefringence -frozen	0	1	0	0	
LIVER	# Ex	10	10	10	10
Vacuolation, centrilobular	0	3	7**	2	
ICN Occasional/multiple	9	4	5	8	
Foci inflammatory cells	10	10	9	10	
Necrosis, focal	4	1	1	0	
Histiocytosis, focal pigmented	0	4*	7**	3***	
Micro granuloma, few	0	7**	10***	6**	
Micro granuloma, many	0	0	0	4*	
LYMPH NODES-CERVICAL	# Ex	9	10	10	9
Histiocytosis, minimal	0	0	0	2	
LYMPH NODES-MESENTERIC	# Ex	10	10	10	10
Histiocytosis, minimal	1	1	3	0	
Histiocytosis, mild	1	9***	6*	1	
Histiocytosis, moderate	0	0	0	8***	
Histiocytosis, marked	0	0	0	1	
Pigmented macrophages	7	0	0	0	

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUBJECT: Incidence of M.N-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-1205R
DAYS : ALL

FATES: ALL
SEX: MALE

GROUP:	Control	64 ZX	MP ZX	LMP ZX
NUMBER OF ANIMALS:	10	10	10	10

OTHER TISSUES AND LESIONS:

MESENTERY- necrotic fat

#	#	#	#
1	0	0	0

Table 42. Histological findings in female rats on the main study fed either control diet, paraffin wax 64 at levels of 0.02%, 0.2% or 2.0%, micro/paraffin wax mixture at levels of 0.02, 0.2% or 2.0% or low melting point wax at a level of 2.0%

The individual findings are shown in Appendix 38.

(* = $p \leq 0.05$; ** = $p \leq 0.01$; *** $p \leq 0.001$)

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OPH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT NO. NO: 3-1203		FATES: ALL							
SEX: ALL		SEX: FEMALE							
GROUP		Control	54 C.02X	64 0.2X	64 2X	MP 0.02X	MP 0.2X	MP 2X	LMP 2X
NUMBER OF ANIMALS:		20	20	20	20	20	20	20	20
HEART/VALVE		#	#	#	#	#	#	#	#
Valve Mitral/tricuspid - frozen	# Ex 5	0	0	0	5	0	0	5	5
Valve Inflammation - HE	0	0	0	0	5**	0	0	5**	5**
	1	0	0	0	2	0	0	5*	5*
LIVER		# Ex 20	20	20	20	20	20	20	20
Vacuolization, peri-portal	1	8**	5	15***	3	15***	19***	19***	
ICH Scattered/multiple	6	12	12	19***	15**	19***	10	4	
Foci Inflammatory cells	13	18	20**	19*	20**	20**	10	4	
Steatosis, focal	1	1	1	0	0	1	0	0	
Micro granuloma, few	0	1	15***	3	0	12***	15***	0	
Micro granuloma, many	0	0	2	16***	0	0	5*	19***	
Granuloma, few	0	0	0	6*	0	0	13***	15***	
Granuloma, many	0	0	1	1	0	0	0	3	
VAG VAGINA-CERVICAL		# Ex 20	20	20	19	20	20	20	18
Metaplasia, minimal	0	1	3	6**	0	0	8**	5*	
Metaplasia, mild	0	0	0	6**	0	0	7**	5*	
Metaplasia, moderate	0	0	0	1	0	0	2	4*	
Metaplasia, marked	0	0	0	0	0	0	1	4*	
VAG VAGINA-REPRODUCTIVE		# Ex 20	20	20	20	20	20	20	20
Metaplasia, minimal	2	9*	2	1	9*	9*	0	0	
Metaplasia, mild	1	10**	9**	10**	1	8**	1	0	
Metaplasia, moderate	0	1	8**	8**	0	3	9***	0	
Metaplasia, marked	0	0	1	1	0	0	10***	20***	
Pigmented macrophages	5	0	0	0	6	0	0	0	

DRAFT

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-1205
DAYS : ALL

FATES: ALL
SEX: FEMALE

GROUP:	Control	64 0.02%	64 0.2%	64 2%	MP 0.02%	MP 0.2%	MP 2%	LMP 2%
NUMBER OF ANIMALS:	20	20	20	20	20	20	20	20
OTHER TISSUES AND LESIONS:	#	#	#	#	#	#	#	#
THYMUS-	2	0	0	0	0	0	0	0
OVARY-	0	0	1	0	0	0	0	0
UTERUS-dilated	0	0	1	0	1	1	1	1
BLADDER-injection site	0	0	0	0	0	0	1	0
DIAPHRAGM-	0	0	0	1	0	0	0	0

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Table 43. Histological findings in female rats on the reversal study fed either control diet, paraffin wax 64 at a level of 2.0%, micro/paraffin wax mixture at a level of 2.0% or low melting point wax at a level of 2.0%

The individual findings are shown in Appendix 39.

(* = $p \leq 0.05$; ** = $p \leq 0.01$; * $p \leq 0.001$)**

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-1205R	FATES: ALL			
DAYS : ALL	SEX: FEMALE			
GROUP:	Control	64 ZX	MP ZX	LMP ZX
NUMBER OF ANIMALS:	10	10	10	10
	#	#	#	#
HEART	# Ex 5	5	5	5
Focal myocarditis	0	0	1	0
Valve inflammation -H&E	0	3	5**	5**
Valve birefringence -frozen	0	1	0	3
LIVER	# Ex 10	10	10	10
Vacuolation, peri-portal	0	3	4*	0
LYMPHOMA	0	0	1	0
ICN Occasional/multiple	5	10*	6	0
Foci inflammatory cells	9	10	9	10
Necrosis, focal	1	0	4	0
Histiocytosis, focal pigmented	0	10***	7**	10***
Micro granuloma, few	0	2	8***	4*
Micro granuloma, many	0	8***	1	6**
LYMPH NODES-CERVICAL	# Ex 9	10	9	10
Histiocytosis, minimal	0	5*	2	6**
Haemorrhagic	0	0	1	0
LYMPHOMA	0	0	1	0
LYMPH NODES-MESENTERIC	# Ex 10	9	10	10
Histiocytosis, minimal	4	0	0	0
Histiocytosis, mild	0	2	8***	0
Histiocytosis, moderate	0	4*	2	~
Histiocytosis, marked	0	3	0	8***
Pigmented macrophages	9	1	0	0
LYMPHOMA	0	0	1	0

Histopathological findings for male and female rats fed with mineral waxes identified as paraffin wax 64 (OFH-064) and a micro/paraffin wax mixture.

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 3-1205A
DAYS : ALL

FATES: ALL
SEX: FEMALE

GROUP:	Control	64 ZX	MP ZX	LMP ZX
NUMBER OF ANIMALS:	10	10	10	10

OTHER TISSUES AND LESIONS:	#	#	#	#
LUNG- LYMPHOMA metastases	0	0	1	0
UTERUS- dilated	1	0	0	0

- A1 -

Appendix 1. Specification analysis provided by the sponsor for the test article used on study 3.1205

Wax sample for BIBRA study 064

Wax type: High Melting intermediate paraffin wax CAS 64 742-51-4

	UNIT	METHOD	
Color		ASTM D-1500	L 0.5
Penetration at 25°C	0.1mm	ASTM D-1321	19
Penetration at 40°C	0.1mm	ASTM D-1321	58
Congealing point	°C	ASTM D- 938	64
Drop melting point	°C	ASTM D- 127	65.1
oil content	%	ASTM D- 721	0.5
Viscosity at 100°C	mm ² /s	ASTM D- 445	6.3
Density at 100°C	kg/cbm	ASTM D-1298	773.0
Ash content	%	ASTM D- 482	<0.01
Refractive index at 100°C		ASTM D-1747	1.4292
sulfur content	ppm	ASTM D-2622	10
Acidity/alkalinity		USP-XXIII	pass
UV absorbance:		FDA-172.826	
280 - 289 nm			pass
290 - 299 nm			pass
300 - 359 nm			pass
360 - 400 nm			pass
Arsenic	ppm	AAS	<1
Chromium	ppm	AAS	<1
Cadmium	ppm	AAS	<1
Lead	ppm	AAS	<1
Carbon nr. distribution of n-alkane content		EWF GC-method	C 21 - C 49
Non-normal paraffin content	%	EWF GC-method	44

GRADE RATES FOR LOWLAND 20-UNIT FERTILIZER GRADE

Test type			Low melting point max	High sulphur max	High melting point max
Abbreviations			LMPW	HSW	HMPW
	Unit	Method			
Color		ASTM D-1500	L 0.5	L 0.5	L 0.5
Penetration at 25°C	0.1mm	ASTM D-1321	18	27	13
Penetration at 40°C	0.1mm	ASTM D-1321	83	101	29
Coagulating point	°C	ASTM D- 938	53.5	74.5	85.0
Drop melting point	°C	ASTM D- 127	55.6	82.0	91.4
O ₂ content	%	ASTM D- 721	0.1	1.8	1.3
Viscosity at 100°C	mm ² /s	ASTM D- 445	3.3	13.7	15.4
Density at 100°C	kg/m ³	ASTM D-1298	751.5	794.4	789.2
Ash content	%	ASTM D- 482	<0.01	0.01	<0.01
Refractive index at 100°C		ASTM D-1747	1.4230	1.4404	1.4393
Sulfur content *	% ppm	ASTM D-2622	5	0.21	77
Acidity/alkalinity		USP-XXIII	pass	pass	pass
UV absorbance:		FDA-172.086			
280 - 289 nm			pass	pass	pass
290 - 299 nm			pass	pass	pass
300 - 355 nm			pass	pass	pass
360 - 400 nm			pass	pass	pass
Arsenic **	ppm	AAS	<1	<1	<1
Chromium **	ppm	AAS	<1	<1	<1
Cadmium **	ppm	AAS	<1	<1	<1
Lead **	ppm	AAS	<1	<1	<1
Carbon nr. distribution of n-alkane content ***		ENF GC-method	C19 - C42	C20 - C74	C22 - C80
Non-normal paraffin content. ***	%	ENF GC-method	11	52	28

Remarks:

* Analysis by Caleb Brett

** Analysis by INO

*** Analysis by OCA

All other analysis by Wilco-Holland

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