

CONTAINS NO CBI

EXXON COMPANY, U.S.A.

POST OFFICE BOX 2180 • HOUSTON, TEXAS 77252-2180



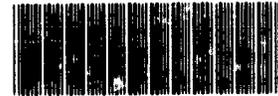
HEALTH SERVICES DEPARTMENT
KENNETH G. GOULD, JR., M.D., Ph.D.
MEDICAL DIRECTOR

8-PP

August 14, 1992

3EHQ-0892-6198 init

Document Control Offer
Chemical Information Division
Office of Toxic Substances
Environmental Protection Agency
401 M Street SW
Washington, D. C. 20460



88928004844

Dear Document Control Officer:

Exxon Company, U.S.A., on behalf of Exxon Corporation, is filing this report in compliance with Section 8(e) of the Toxic Substance Control Act. Exxon, one of several participating member companies of a toxicology study sponsored by CONCAWE (the Oil Companies' European Organization for Environment and Health Protection), has recently received a final report of toxicology test results from a 90-day feeding study in Fischer 344 rats. The study 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 was a material defined as "Low Melting Point Wax". The low melting point wax has been further described as low melt point paraffin wax (no CAS number defined). Exxon USA is a domestic refiner of hydrotreated paraffin wax, which shares similar physical/chemical properties to the tested material.

In general, focal inflammatory lesions were observed in the mitral valve of the heart in the high dose (2.0% wax in the diet) male and female groups, and in the next highest dose (0.2%) female group alone; the findings were statistically significant. No significant incidence of mitral valve heart lesions were observed in the two lowest treatment groups (0.02 and 0.002%) nor in the control group. A significant incidence of the heart lesion was also observed in both male and female rats treated with 2.0% wax in the diet for 90 days, and then untreated for 28 days to determine reversibility of effects. The toxicological significance of this unusual lesion is not known.

Other biological findings of note for the low melting point wax were granulomatous-type formations in the liver of both males and females of the two highest doses (2.0 and 0.2%) and an occurrence of histiocytes in the mesenteric lymph nodes. Similar findings have been previously reported to occur following dietary administration of certain other mineral hydrocarbons in the liquid form.

Document Control Officer

-2-

August 14, 1992

2

Exxon has summarized these findings and the summary document is attached. An earlier draft of the CONCAWE/BIBRA study results was previously submitted to the Administrator by the American Petroleum Institute, and a recent copy of the latest report of this study was also submitted to the Administrator by the American Petroleum Institute as a For Your Information submission. The significance of all of the above findings to humans remains unclear.

If you require additional information, please call Steve Killiany (713/656-3904) or me (713/656-3704).



KGG/SEK:ccr
Attachment
sek/9-day.api

0 0 - 0 3

M

**EXXON BIOMEDICAL SCIENCES, INC. SUMMARY
HISTOPATHOLOGIC FINDINGS FROM A 90-DAY FEEDING STUDY
OF A LOW MELTING POINT WAX IN FISCHER 344 RATS**

AUGUST 7, 1992

CONCAWE (The Oil Companies' European Organization for Environment and Health Protection) has sponsored a 90-day toxicity study of food grade mineral hydrocarbons which included a low melting point paraffin 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 at dose levels of 0.002%, 0.02%, 0.2% and 2.0%.

In the final report dated 23 July 1992, male and female rats fed the higher dose of low melting point paraffin wax were reported to have focal inflammatory lesions within the cusps of the mitral valve. The lesion was described as confined to the mitral valve and did not extend to the myocardium. The BIBRA report described these findings as follows: "Focal inflammatory lesions were observed within the cusps of the mitral valve. The lesion was characterized by an increased cellularity of the valve with destruction of the fibrous core. The increased cellularity was composed of a mixed population of macrophages, plasma cells and lymphocytes. In many lesions mitotic figures could be identified." This lesion was found in 11/20 male and 11/20 female rats at the 2.0% feed level, and in 5/20 female rats at the 0.2% feed level. The lesion was observed in 1/60 control group male rats. "Following a 28 day reversal period there was still a statistically significant incidence of the heart lesion in both male and female animals." The toxicologic significance of this lesion is unknown. To the best knowledge of the scientists working on this project, this association with the administration of these specific mineral hydrocarbons to animals is heretofore unrecognized. A significant incidence of this lesion was not observed in male or female rats fed concurrently any of eight other mineral hydrocarbon products, including six white oils and two microcrystalline waxes, at similar dose levels.

Other histopathologic findings were also found in rats fed a diet which contained the low melting point paraffin wax. In general, these findings included microgranuloma/granuloma formation in the liver at the 2.0% and 0.2% feeding levels and a dose-dependent (0.002 to 2.0%) occurrence of histiocytosis in the mesenteric lymph nodes. These effects were seen in both sexes, but more so in female rats. Similar findings have been previously reported to occur following dietary administration of certain other mineral hydrocarbons in the liquid form.

An earlier draft of the CONCAWE/BIBRA study results was previously submitted to the Administrator by the American Petroleum Institute as a For Your Information submission. The significance of these findings to humans remains unclear but is under active investigation.

RESULTS

Heart

Focal inflammatory lesions were observed within the cusps of the mitral valve. The lesion was characterized by an increased cellularity of the valve with destruction of the fibrous core. The increased cellularity was composed of a mixed population of macrophages, plasma cells and lymphocytes. Pyknotic nuclei and cell debris were scattered throughout the lesions. In many lesions mitotic figures could be identified.

In the high dose low melting point wax group 11/20 male and 11/20 female animals were observed to have the lesion. Subsequent to the observation of the lesion in the high dose group the 0.2, 0.02 and 0.002% low melting point wax groups were examined. The only statistically significantly increased incidence of the lesion was observed in the female 0.2% group (5/20 animals). The lesion was present in 1/60 male control animals and in occasional males from the high dose treatment groups. The lesion was not observed in any of the female controls or other female treatment groups.

Following a 28-day reversal period there was still a statistically significantly increased incidence of the heart lesion in both male and female animals treated with low melting point wax although the incidences were lower than at the end of the treatment period.

DISCUSSION

An inflammatory lesion of the mitral valve of the heart was observed in the 2.0% (male and female) and 0.2% (female only) low melting point wax groups. There was no significant incidence in animals receiving any of the other treatments. The lesion was confined to the mitral valve and was not associated with focal inflammatory lesions of the myocardium. The toxicological significance of this unusual lesion is not known.

0 0 0 5

BIBRA

3.1010

The attached tables were taken from the BIBRA Toxicology International Final Report:

STUDY TITLE

A 90-day feeding study in the rat with six different white mineral oils (N15 (H), N70 (H), N70 (A), P15 (H), N10 (A) and P100 (H)), three different mineral waxes (a low melting point wax, a high melting point wax and a high sulphur wax) and coconut oil

AUTHOR

N.R. Worrell

STUDY COMPLETED ON

23 July 1992

PERFORMING LABORATORY

BIBRA Toxicology International
Woodmansterne Road
Carshalton
Surrey
SM5 4DS UK

SPONSOR

CONCAWE
Madouplein 1
B-1030 Brussels
Belgium

LABORATORY PROJECT IDENTITY

Project No. 3.1010

Report No. 1010/3/92

0 0 0 6

PROJECT SUMMARY TABLE 51
SUMMARY: Incidence of Non-Neoplastic Microscopic Findings

PROJECT IDENTIFICATION: 3.1010

FATES: ALL

DAYS: ALL

SEX: MALE

STUDY: MAIN

TREATMENT:

DOSE: (% in diet)

NUMBER OF ANIMALS:

Control	0.002	0.02	0.2	2.0	R
0	20	20	20	20	2.0
60	20	20	20	20	10

	#	#	#	#	#	
AORTA	# Ex	60	0	0	0	20
VEIN	# Ex	60	0	0	0	20
KIDNEY	# Ex	60	20	20	20	20
Glomerulosclerosis		0	0	0	0	0
Glomerulonephrosis a1		4	0	1	0	1
Glomerulonephrosis mod		0	0	0	0	0
Tubular basophilia		36	6	3	4	6
Inflammation cortical		1	0	0	0	0
Focal scar		0	0	0	0	0
Eosinophilic vacuolation tub.		0	0	0	0	0
Lymphocytic infiltration		0	0	0	0	0
HEART	# Ex	60	20	20	20	20
Foci necrosis/inflam. cells		22	2	1	0	7
Coronary artery-periarteritis		0	0	0	0	0
Subendocardial necrosis lt. ven		0	0	0	0	2
Inflammation base mitral valve		1	0	0	1	11***
Haemociderin base mitral valve		0	0	1	0	0
LIVER	# Ex	60	20	20	20	20
Vacuolation CL		0	0	1	0	20***
Vacuolation PP		0	0	0	4**	0
Vacuolation diffuse		0	0	0	0	0
Vacuolation focal		0	0	0	1	0
ICN Occasional/multiple		47	15	17	12	9
Foci inflammatory cells		50	15	16	18	7
Inflammation peribil lg duct		0	1	0	0	0
Subcaps area chronic inflam		0	0	0	0	0
Necrosis subcapsular		2	0	0	0	0
Micro granuloma Few		0	0	0	15***	7***
Micro granuloma Many		0	0	0	1	8***
Granuloma Few		0	0	0	2	2
Granuloma Many		0	0	0	0	3*
LUNG	# Ex	60	20	20	20	20
Peribronchial lymphocytes		45	11	14	14	11
Perivascular lymphocytes		29	12	9	5	1
Inflammation focal		43	5	13	13	15
Foci alveolar macrophages		11	2	2	5	1
Alveolar thickening		2	0	0	0	0
Occasional microgranuloma		0	0	0	0	1
Granuloma		0	0	0	0	0
BRAIN	# Ex	60	0	0	0	20
SPINAL CORD	# Ex	60	0	0	0	20
EYE	# Ex	60	0	0	0	20

PROJECT SUMMARY TABLE 53

SUMMARY: Incidence of Non-Neoplastic Microscopic Findings

PROJECT IDENTIFICATION: 3.1010		FATES: ALL				
DAYS: ALL		SEX: FEMALE				
STUDY: MAIN						
TREATMENT: Main Study		Control	Low Melting Point Wax			R
DOSE: (% in diet)		0	0.002	0.02	0.2	2.0
NUMBER OF ANIMALS:		60	20	20	20	20
		#	#	#	#	#
AORTA	# Ex	60	0	0	0	20
VEIN	# Ex	60	0	0	0	20
KIDNEY	# Ex	60	20	20	20	20
Glomerulonephrosis al		0	0	0	0	0
Glomerulonephrosis mod		0	0	0	0	0
Tubular basophilia		5	0	0	0	0
Nephrocalcinosis cort/med		3	0	0	0	0
Calcinosis		0	0	0	0	0
HEART	# Ex	60	20	20	20	20
Foci necrosis/inflam. cells		6	2	0	0	2
Foci intra calcification		0	0	0	0	0
Inflammation base mitral valve		0	1	1	5***	11***
Endocarditis		0	0	0	0	0
LIVER	# Ex	60	20	20	20	20
Vacuolation CL		0	0	0	0	0
Vacuolation MZ		0	0	0	0	0
Vacuolation PP		4	11***	5*	5*	19***
Vacuolation focal		0	0	1	0	0
ICN Occasional/multiple		37	5	0	0	0
Foci inflammatory cells		48	12	16	0	1
Foci vac hepatocyte deg		0	0	0	0	1
Inflammation peribil lg duct		0	0	0	1	0
Necrosis focal		0	0	0	0	0
Necrosis subcapsular		0	0	0	0	0
Necrosis extensive		0	0	0	0	0
Micro granuloma Few		0	0	0	7***	0
Micro granuloma Many		0	0	0	2	14***
Granuloma Few		0	0	0	6***	0
Granuloma Many		0	0	0	4**	5***
Granuloma Focal		0	0	0	0	0
Lymphocytic infil ass gran mar		0	0	0	3*	4**
Cyst keratinised		0	0	0	0	0
Focus clear cell		0	0	0	0	0
Fibrosis peribiliary		0	0	0	0	0
Telangiectasis		0	0	0	0	0
LUNG	# Ex	60	20	20	20	20
Peribronchial lymphocytes		47	11	13	11	10
Perivascular lymphocytes		10	0	4	2	0
Inflammation focal		10	3	5	1	8*
Foci alveolar macrophages		4	0	0	2	0
Alveolar thickening		0	0	0	0	0
Occasional microgranuloma		0	0	0	0	0
BRAIN	# Ex	60	0	0	0	20

0008

8

FOOTNOTES

Asterisks:

Incidences marked with asterisks are significantly increased compared with control incidences (Fisher's exact test * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Incidences with differing severity were compared with control incidences using a one-sided Mann Whitney U test. Incidences bracketed and marked with an asterisk are significantly increased compared with control incidences (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

The individual findings are shown in Appendix 58.

R:

Observations for Reversal Period

92 SEP -3 PM 2:56

0010

CERTIFICATE OF AUTHENTICITY

THIS IS TO CERTIFY that the microimages appearing on this microfiche are accurate and complete reproductions of the records of U.S. Environmental Protection Agency documents as delivered in the regular course of business for microfilming.

Data produced 12 23 92 Marcia Libalino
(Month) (Day) (Year) Camera Operator

Place Syracuse New York
(City) (State)

