Message

From: Jon Heylings [redacted]
Sent: 11/19/2018 3:50:42 PM
To: Cook Andy GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b012593ccd764559b2f9986da61a2e8f-Cook Andy A]
CC: Travis Kim GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1528a9bee5884668b9ecf5910b6709f0-Travis Kim]; Botham Phil GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=675e0b3a54374a76b913a2fb682de1b2-Botham Phil]
Subject: FW: ICI PHARMACEUTICALS REPORT
Attachments: 19. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 Front Cover.pdf; 20. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 PH18987C Chemistry.pdf; 21. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 PH23516C Pig.pdf; 22. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 PH23516C Primates.pdf; 23. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 PH20992C Human - Subject Details.pdf; 24. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 PH20992C Human - Blood Levels.pdf; 25. Paraquat Emetic - Extracts from Pharms Reports on ICI 63,197 (PP796) Jan 1990 PH20992C Human - Nausea and Emesis.pdf

Importance: High

Dear Andy,
Now that I have returned from holiday and have access to my scanner here at Keele University, here is the report with Extracts of the various ICI Pharmaceuticals studies on ICI 63197 (PP796), including the key one below, that you and Kim have both requested in separate memos.

Bayliss, P F C (1973) A summary of clinical results of the phosphodiesterase inhibitor ICI 63,197 in a variety of disease states. ICI Pharmaceuticals Report No. PH20992B.

I have scanned every page of the Extracts document that Pharms Report Centre put together back in 1990. This includes vomiting observations in pigs, primates and man. I have labelled these as Emetic files 19-25 since this follows the 18 files on the topic I handed over to you at Jealotts Hill on October 31st. There are other quite sensitive memos in my personal files between myself and Senior staff who were in charge of this area at the time. I can reassure you that I am not party to any information that disputed my own findings as I explained to you, Kim Mathew and Phil at our meeting in October. The key document amongst the attached PDFs is Emetic File No. 25, which features in my memos to my Line Manager and the CTL Executive back in 1990 on the incidence and timing of emesis in the human volunteer study with 7 doses of ICI 63,197. This is the table that was "edited" by Mike Rose to suit his own and the Agrochemicals Business needs back in the 1970s.
I fully understand the need for the Agrochemicals Business to corroborate my own observations on the original studies conducted by ICI Pharmaceuticals. This is a scientific matter between ourselves at this stage. However, now that I am aware that there is still incorrect and misleading information in the current FAO specification for the emetic in commercial paraquat products. This is coupled with Syngenta's unwillingness to introduce a more costly Inteon type product with higher emetic levels, or even to simply dilute the product concentrate with water, I think we all have a moral and ethical responsibility to discharge this information to our contacts in the International Pesticide Registration arena and perhaps also PAN. I am sure you understand my position on this since something needs to be done.
I assume you will inform the Senior Syngenta Executives and Legal Teams in Guildford, Greensboro and Basel of the situation, once you are satisfied that my own observations are correct. Syngenta and its former businesses have provided me with a great career over more than 30 years. This is not personal its just my thoughts of those very young accidental victims of paraquat poisoning in the Cal EPA publication that I am losing sleep over. If the Company had dealt with this in a responsible and ethical manner back in the 1990s we would not be having this dialogue in 2018. Syngenta clearly had the option to introduce a "safer" formulation with an effective emetic level in a minimum lethal dose in man but chose not to do so and continue to ratify incorrect information in the United Nations FAO Specification for paraquat products.

I look forward to hearing your collective views on this important matter in due course, I am happy to be involved with any further meetings with others on this matter, as you see necessary.

Yours faithfully

Jon Heylings

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Jon Heylings
Sent: 09 November 2018 15:29
To: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Subject: Re: ICI PHARMACEUTICALS REPORT

Hi Andy,
Thanks for your email. As I explained to Kim yesterday when he asked me the same question, yes I do have the information you require. During my investigations in 1990, I requested copies of various pages and Tables in the ICI Pharmaceuticals reports I had studied on the emetic ICI 63197 in the Pharms Report Centre at Alderley Park. Obviously, the full reports on clinical trials were very large and I only needed certain information to establish the incidence of vomiting in the human volunteer study by Bayliss PFC (Report No. PH20992) that was undertaken in the 1970s. I asked the Reports Centre at Pharms to compile these "Extracts" independently for specific pages in the reports in a Category C report, once I had established there was a potential mis-match issue between what was in the Rose report CTL/R/390 R and the Bayliss report (PH20992). This is the "Extracts from reports on ICI 63,197" - the orange cover of which I showed you. The Extracts also contained the emetic effects in pigs and primates, in addition to the key Bayliss human volunteer data that we discussed last week.

I already promised to send a scan of the PH20992 pages to Kim when I am back at DTL on November 19th, since I don't have a scanner at home and I am now on leave all next week. I will copy you in with my response to Kim. The scans will contain the following information:

Details of the 12 human volunteers who took the ICI 63197 drug (age, sex, body weight and dose).
Blood levels of ICI 63197 in micrograms/ml - every hour from 1 hour to 8 hours.

Side effects at each dose level including whether the volunteer had nausea, whether they vomited and exactly when.
Conclusions from the volunteer study

As I explained at Jealotts Hill on October 31st, the 4/37 vomiting response for a 2mg dose of ICI 63197 in the Rose report is not in the PH20992 report data I will be sending you. It replaced the 2mg dose in the volunteer study and originated from a completely separate human clinical trial on a specific disease. The details of this are in the correspondence between myself and the Head of Regulatory Toxicology at the time (in the files I gave you). As I explained, this was not in fact an incidence of vomiting of 4/37 (11%), it was 4/1356 (0.3%) at the 2mg dose.

You will see that this information I will be sending you tallies with the Table I reproduced on PH20992 for Lewis Smith in my memo of September 5th 1990. I fully understand that you need to see the actual table in the ICI Pharms report for thoroughness and, indeed, you may wish an independent verification of this information directly from AstraZeneca. In retrospect, I am glad that I obtained the original data at the time of my own scientific investigation and prior to the various demergers and mergers.

What really concerns me are the implications for Syngenta if registration approval for paraquat-containing products was maintained in certain territories on the basis of introducing an ineffective concentration of emetic in man. What is potentially more damaging is that this was not acted upon in the 1990s when there was clear evidence in human poisoning surveys that the emetic was ineffective at the level in the FAO specification and that ICI Agrochemicals were now aware that the the original effective dose in man was, in fact, fabricated.

I would really like to be proved wrong on this, but when I piece it all together with the high level investigations that never reported, the staff who left, and the reluctance to really grasp Inteon as a way to introduce an effective emetic, it all makes sense to me. The Agrochemicals business were aware of these issues but were not prepared to bear the cost of introducing a safer formulation.

Regards
Jon

Jon R Heylings
Professor of Toxicology
DTL, Keele University

From: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Sent: 09 November 2018 11:59:04
To: Jon Heylings
Subject: ICI PHARMACEUTICALS REPORT

Dear Jon,

As you will have already gathered from Kim we are trying to source some relevant reports, we would like to take the quickest route to accessing the data. As part of this process could you

advise as to whether or not you currently have a copy of the following ICI Pharmaceuticals report:

Bayliss, P F C (1973) A summary of clinical results of the phosphodiesterase inhibitor ICI 63,197 in a variety of disease states. ICI Pharmaceuticals Report No. PH20992B.

If not, do you recollect a copy of this report ever having been held within CTL?

Thanks and regards.

Andy

REPORTS COLLECTION
RECEIVED: 25 Jan 90
COPY No.

FILE No.
PH 18987C p 2
PH 23510C p 2, 3
PH 20992C p 5, 6, 11
C

ICI Pharmaceuticals

TITLE :- Extracts from reports on ICI 63,197

AUTHOR(S) :-

DATE :-

CATEGORY C REPORT

(COMPANY SECRET)

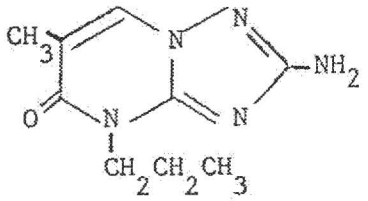
NOT TO BE PHOTOCOPIED

For additional copies please consult Reports Collection

3. NAMES

(i)	Approved Name	:	Not yet selected
(ii)	Laboratory Code Number	:	I.C.I. 63,197
(iii)	Chemical Name	:	2-Amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine

4. DESCRIPTION

(i)	Physical form	:	A white to pale cream powder
(ii)	Solubility	:	Soluble in 500 parts of water, in 12 parts of chloroform and in 170 parts of alcohol (95%).
(iii)	Structural formula	:	
(iv)	Molecular formula	:	$C_9H_{13}N_5O$
(v)	Molecular weight	:	207.2

5. INTENDED USE

Evaluation of efficacy in the treatment of mental disease and respiratory disease.

PH23516C

ICI 63,197 : EMETIC PROPERTIES IN PIGS, MONKEYS AND MARMOSETS

1. PIGS

Groups of eight 40 - 50 lb. pigs were fed a standard pig-fattening ration, containing concentrations of ICI 63,197 ranging from 4 to 40 g/long ton. This was calculated so that ingestion of 500 g. diet would provide dose levels of ICI 63,197 of 0.1 - 1.0 mg/kg to 20 kg pigs. The pigs were provided with 500 g of the medicated diet twice daily for 2 days, and observed for quantity of food eaten and emesis. The results are given in the following table.

Dosage level		Number of Pigs	Response after 2 feeds		
Concentration in diet	mg/kg/pig		Refused diet	Emesis	Slow eating
40 g/ton	1.0	8	8	5	-
20 g/ton	0.5	8	8	3	-
10 g/ton	0.25	8	6	0	2
4 g/ton	0.1	8	0	0	8

2. MONKEYS AND MARMOSETS

Seven Rhesus Monkeys and two marmosets were dosed with ICI 63,197 on varying numbers of occasions, and observed for clinical signs.

The compound was administered by stomach tube as a suspension in an inert dispersing agent*, diluted with water as necessary, except where otherwise indicated.

The results are given in detail on the following pages. A summary of the emetic response to various oral doses of ICI 63,197 is given in the following table:-

Dose (mg/kg oral)	Number of administrations	Number of emeses	% emeses
0.025	6	2	33
0.05	5	0	0
0.1	24	5	21
0.2	19	8	42
0.3	15	2	13
0.4	15	5	33
0.5	5	4	80
0.6	2	2	100
1.0	2	2	100

*'Lissapol' NX (Nonylphenolethylene oxide condensate)	0.1%
'Lissapol' C (Sodium salt of sulphated cetyl/oleyl alcohol mixture)	0.1%
'Dispersol' OG (Polyglyceryl ricinoleate)	0.1%
Distilled water	to 100.0%

RESULTS

Details of subjects studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Dose ICI 63,197 (mg)
1	ML	23	F	50.5	0.25
2	IL	22	M	77.5	0.5
3	HMcD	21	M	65.5	1
4	PL	22	M	74.0	1
5	MM	20	F	56.5	2
6	IMcL	24	F	56.0	2
7	N	22	F	55.0	2
8	PR	21	M	79.0	3
9	C	23	M	72.0	3
10	APC	21	M	82.5	4
11	CB	23	M	80.0	4
12	CC	21	M	80.0	8

Blood levels of ICI 63,197

These are shown below (μg/ml.):-

No.	Dose of ICI 63,197 (mg)	Time (hrs.)							
		1	2	3	4	5	6	7	8
1	0.25	0.016	0.006	0.004	0.005				ND
2	0.5	0.008	0.017	0.005	0.005				ND
3	1.0	0.005	0.019	0.004	0.006		0.005		0.004
4	1.0	0.017	0.016	0.009	0.006		0.008		
5	2.0	0.018	0.034	0.024	0.018		0.007		
6	2.0	0.034	0.065	0.044	0.039		0.015		0.006
7	2.0	0.062	0.068		0.056	0.044	0.037	0.031	0.025
8	3.0	0.044	0.031			0.006		0	0
9	3.0	0.050	0.056		0.044	0.031		0.018	0.025
10	4.0	0.081	0.041	0.034	0.060		0.01		0.014
11	4.0	0.045	0.056	0.044	0.033		0.016		0.009
12	8.0	0.047	0.085	0.068	0.041		0.029		0.042

ND = not detected, i.e. < 0.004 μg/ml.

The half life varies from $1\frac{1}{2}$ - $3\frac{1}{2}$ hours in this series.

Possible side effects

These are shown below:-

No.	Dose(mg.)	Possible side effects
1	0.25	Nil.
2	0.5	Mild nausea and light headedness.
3	1.0	Nausea at 1 hour.
4	1.0	Severe dizziness at 15 minutes. Felt as if he had taken "pep pills" from 1 - 4 hours.
5	2.0	Mild nausea.
6	2.0	Nil.
7	2.0	Dizziness and sweating at 30 minutes followed by some nausea.
8	3.0	Dizziness and nausea marked ¾ - 2 hours.
9	3.0	At 30 minutes dizzy, pale, sweating. Nausea marked.
10	4.0	Nausea and flushing at 15 minutes. Vomited at 30 minutes. Light headedness for 2 - 3 hours.
11	4.0	Dizziness, flushing of face, sweating from ½ - 2 hours.
12	8.0	At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours.

V 05

V 2

CONCLUSIONS

No clearly defined results emerged from this study, although certain suggestive ones were seen. The following points may be made:-

(1) The half life of ICI 63,197 in the human, following a single oral dose is between 1½ and 3½ hours.

(2) No clear effect was seen on pulse rate, although a slight fall was seen in some subjects. Similarly, no clear effect was seen on blood pressure, although in some subjects a fall was seen in the 2 - 4 hour period.