Introduction:

A process for the synthesis and purification of Indocyanine Green ("ICG", CAS Number 3599-32-4) is scheduled to be introduced at TopChem Pharmaceuticals, Ballymote Business Park, Carrownanty, Ballymote, Co Sligo during Q1 2022. Indocyanine Green is a diagnostic agent used in medical and surgical procedures.

Manufacturing Process:

The manufacturing process consists of three synthetic steps and a final purification. In The first step 1,1,2-Trimethylbenz[e]indole and 1,4-butane sultone are heated with propylene carbonate as solvent to form the intermediate salt ICG-1. This salt (ICG-1) is then reacted with N-[5-(Phenylamino(-2,4-pentadienylidene]aniline monohydrochloride in acetic anhydride solution to form the intermediate ICG-2. This ICG-2 is then reacted with a further molecule of ICG-1 with the reagents, triethylamine and sodium iodine with ethanol as the reaction solvent to form the crude Indocyanine Green. Indocyanine Green is then purified by treatment with isopropanol and water followed by vacuum drying. All operations will be performed on a laboratory scale within fume hoods. Approximate batch sizes for this product will be ~ 2Kg and use max 20L vessels. Total output per annum is anticipated at 10 kilos.

Material Information:

Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. № or Code	Material/ Substance	CAS Number	Danger (1) Category	Amount Stored (tonnes)	Annual Usage (tonnes)	Hazard Statements	Precautionary Statements	Nature of Use
	1,1,2-Trimethylbenz[e]indole	41532-84-7		0.03	0.01	H315 H335 H319	P261 P302+P352 P280 P305+P351+P338	Starting material
	1,4-Butane sultone	1633-83-6	Harmful if swallowed, irritant	0.03	0.01	H302 H315 H317 H319 H335 H351	P201 P280 P301+P312+P330 P302+P352 P305+P351+P338 P308+P313	Starting material
	N-[5-(Phenylamino(-2,4-pentadienylidene]aniline monohydrochloride	1497-49-0	Irritant	0.03	0.01	H315 H319 H335	P261 P264 P271 P280 P302+P352 P305+P351+P338	Starting material
	Acetic anhydride	108-24-7	Flammable, Corrosive	0.08	0.04	H226 H302 H314 H330	P210 P280 P301+P312 P303+P361+P353	Reagent
	Triethylamine	121-44-8	Highly flammable, Corrosive	0.01	0.005	H225 H302 H311+H331 H314 H335	P210 P280 P301+P312 P303+P361+P353 P304+P340+P310 P305+P351+P338	Reagent
	Sodium Iodide	7681-82-5	Irritant	0.005	0.002	H315 H319 H372 H400	P260 P264 P273 P302+P352 P305+P351+P338 P314	Reagent
	Acetone	67-64-1	Highly flammable, irritant	0.50	0.25	H225 H319 H336 EUH066	P210 P233 P241 P242 P305+P351+P338	Solvent
	Ethanol	64-17-5	Highly flammable, Irritant	0.12	0.06	H225 H319	P210 P233 P240 P241 P242 P305+P351+P338	Solvent
	Isopropanol (IPA)	67-63-0	Highly flammable, Irritant	0.60	0.30	H225 H319 H336	P210 P233 P240 P241 P242 P305+P351+P338	Solvent
	Propylene Carbonate	108-32-7	Irritant	0.08	0.04	H319	P305+P351+P338	Solvent

Notes: 1. c.f. Article 2(2) of SI № 77/

Table G.1(ii) Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. Nº or Code	Material/ Substance	TA Luft Class 1, 2 or 3	Odour			EU Lists I and II (Tick and specify Group/Family Number)			
			Odourous Yes/No	Description	Threshold[3] mg/m³	Dangerous Substances Directive 76/464/EEC		Groundwater Directive 80/68/EEC	
						List I	List II +129	List I	List II
	1,1,2-Trimethylbenz[e]indole	-	No	-	-				
	1,4-Butane sultone	-	No	-	-				
	N-[5-(Phenylamino(-2,4-pentadienylidene]aniline monohydrochloride	-	No	-	-				
	Acetic anhydride	I[1]	Yes	Pungent, irritating	0.12				
	Triethylamine	I[1]	Yes	Pungent, irritating	0.004				
	Sodium Iodide	-	No	-	-				
	Acetone	III[1]	Yes	Sweet, fruity, etherous	11				
	Ethanol	III[1]	Yes	Alcohol	0.26				
	Isopropanol (IPA)	III[1]	Yes	Alcohol	1.1				
	Propylene Carbonate	Not listed	No	Not classed as VOC	-				

1. http://m.bmu.de/fileadmin/Daten_BMU/Download_PDF/Luft/taluft_engl.pdf [1a] Section 5.2.4. Pg 59
2. www.infomil.nl/publish/pages/63235/lvoc-annexviii.pdf (Section 3.2.5)
3. 3M 2010 Respirator Selection Guide

Emissions

EMISSIONS TO ATMOSPHERE - Minor atmospheric emissions

Emission point Reference Numbers	Description	Emission details[1]				Abatement system employed
		material	mg/Nm$^{3(2)}$	kg/h.	kg/year	
E1	Fume Hood 1 Exhaust fan in Production Laboratory	Organic Vapour	<1.3	<0.002	<10	Not Applicable
E2	Fume Hood 2 Exhaust fan in Production Laboratory	N/A	N/A	N/A	N/A	Not used in this process
E3	Fume Hood 3 Exhaust fan in Production Laboratory	N/A	N/A	N/A	N/A	Not used in this process
E4	Fume Hood 4 Exhaust fan in Development Laboratory	N/A	N/A	N/A	N/A	Not used in this process
E5	Local Laboratory Exhaust	N/A	N/A	N/A	N/A	Not used in this process

1. Fume Hood 1 is used for illustration purposes only, however, any one of the Fume hoods 1-3 in the Production Laboratory maybe used in this process.

EMISSIONS TO ATMOSPHERE – Fugitive and Potential atmospheric emissions

Not Applicable – none expected.

Waste Streams:

No gaseous waste will be generated during this process. No solid waste will be generated during this process. All waste will be in liquid form. Liquid waste will be separated into non-chlorinated organic solvents; and acetic anhydride/acetone mother liquors. The acetic anhydride/acetone mother liquors are segregated for safety reasons.

WASTE - Hazardous Waste Recovery/Disposal

Waste material	EWC Code	Main source[1]	Quantity		On-site Recovery/Disposal (Method & Location)	Off-site Recovery, reuse or recycling (Method, Location & Undertaker)	Off-site Disposal (Method, Location & Undertaker)
			Tonnes / month[2]	m^3 / month[2]			
Waste Stream #1 Non-Chlorinated Organic Solvent Waste	070504	Acetone, Ethanol, IPA washes & mother liquors from reactions	0.045	0.055	Not Applicable	Not Applicable	as per Licensed contractor
Waste Stream #2 Acetic anhydride waste, diluted with acetone	070504	ICG-2 reaction – mother liquor and washes	0.012	0.013	Not Applicable	Not Applicable	as per Licensed contractor

1 A reference should be made to the main activity / process for each waste.
2 Total output per annum averaged over 12-month period. Actual monthly figures may vary up or down.

WASTE - Other Waste Recovery/Disposal

Waste material	**EWC Code**	**Main source[1]**	**Quantity**		**On-site recovery/disposal[2]** (Method & Location)	**Off-site Recovery, reuse or recycling** (Method, Location & Undertaker)	**Off-site Disposal** (Method, Location & Undertaker)
			Tonnes / month	m^3 / month			
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

1 A reference should be made to the main activity/ process for each waste.
2 The method of disposal or recovery should be clearly described and referenced to Attachment H.1