

Supporting information

Background information about sildenafil citrate

Sildenafil Citrate, the API in Viagra™, constitutes a selective inhibitor of PDE5 used to prevent the male erectile dysfunction. Initially the drug was targeted for Angina and the active ingredient for the development program was produced using an optimized medicinal chemistry route. The improvements to the Medicinal Chemistry route are fully detailed in literature,* the main changings regarded: i) the substitution of tin based reducing agent (SnCl₂) with a catalytic hydrogenation using palladium, ii) the replacement of the old hydrogen peroxide-based cyclization method with the use of KOBut/tBuOH (100% yield), iii) the introduction of a solvent into the exothermic methylation reaction (molecule 3) and iv) the reduction of thionyl chloride amount (from 1.6 to 1.2 equivalent) by the use of toluene.* However, when the indication moved from Angina to Male Erectile Dysfunction it was difficult to keep up with the material requirements for a rapid clinical and then market expansion and this led Pfizer to investigate a new chemical route. Main improvements concerned (i) introduction of a convergent synthesis (ii) the sole use of water as a solvent in the conversion of 2-ethoxybenzoic acid into sulfonamide derivate (compound 9), (iii) the activation of this intermediate using a relatively cheap reagent such as *N,N'*-carbonyldiimidazole and (iv) improving the yield in the citrate salt forming step to 100% using a statistical design approach. Literature*.16 reports that transition from the medicinal to the commercial route in the case of sildenafil citrate lead to substantial resources reduction which produces an E-factor of 8, lower than average estimated 25 to 100 for the pharmaceutical sector.^{18,19} Moreover, all the efforts made in order to increase the process yield while reducing the solvents amount (around 99.7%, from 1540 to 5 kg/kg API) led in 2003 to the win of the Crystal Faraday Award for green chemical technology by the Institute of Chemical Engineers. As reported previously, a detailed description of all the chemical mechanisms and substances involved in both pathways was already reported in literature.

References

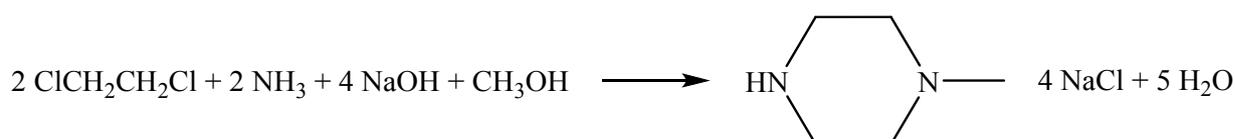
- * P.J. Dunn, in *Process Chemistry in the Pharmaceutical Industry*, ed. K. Gadamesetti and T. Braisch, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2008, vol. 2, ch. 16, pp. 267-277.

LCI improvements: detailed description of the N-methylpiperazine pathway

LCI improvement – Phase I

As reported in manuscript, the first step to fill the data gap in the inventory of chemical is select the main pathway for the target molecule. Organic chemistry suggests that N-methylpiperazine (NMP) is commonly produced by the methylation reaction of the piperazine, $\text{HN}(\text{CH}_2\text{CH}_2)_2\text{NH}$, using methanol as the source of the methyl group.³⁹ Then the second step is to verify if LCI libraries contain default processes which simulate the synthesis of reagents used in the reaction. Unfortunately, Ecoinvent database did not provide any information regarding the industrial synthesis of the piperazine. However, literature³⁸ suggests that piperazine is obtained as co-product in the ammoniation of 1,2-dichloroethane, $\text{ClCH}_2\text{CH}_2\text{Cl}$. The reaction with aqueous ammonia, carried out at high temperature and pressure, results in piperazine and ethyleneamine co-products in the form of amine hydrochloride salts, which is then neutralized by sodium hydroxide with the release of NaCl and free amines.³⁸

Below the total stoichiometric equation which describes the entire pathway is reported



As stated in the manuscript, a *cradle-to-gate* boundaries were considered using an already published standard approach in order to fill the inventory gap for chemicals, assuming: a process efficiency of 95% over the entire stoichiometric equation, air emissions estimated to be 0.2% of the input and the water emissions were evaluated as a difference between unreacted reagents and air releases.³⁶ Therefore, neglecting NaCl and H₂O in waste streams due to their no environmental relevance, the first stage of the inventory was completed using the mass balance reported below calculated assuming the production of 1kg of NMP (100.16 kg/kmol) as a functional unit, which corresponds to almost 9.98E-03kmoles.

Molecular weights (kg/kmol)

1,2-dichloroethane: 98.96

NaOH: 39.99

NH₃: 17.03

CH₃OH: 32.04

System input, process efficiency of 95% over the entire stoichiometric equation

kmol 1,2-dichloroethane = $(9.98\text{E-}03/0.95) * 2 = 2.10\text{E-}02$

kmol NaOH = $(9.98\text{E-}03/0.95) * 4 = 4.20\text{E-}02$

kg 1,2-dichloroethane = $2.10\text{E-}02 * 98.96 = 2.08$

kg NaOH = $4.20\text{E-}02 * 39.99 = 1.68$

kmol NH₃ = $(9.98\text{E-}03/0.95) * 2 = 2.10\text{E-}02$

kmol CH₃OH = $(9.98\text{E-}03/0.95) = 1.05\text{E-}02$

kg NH₃ = $2.10\text{E-}02 * 17.03 = 3.58\text{E-}03$

kg CH₃OH = $1.05\text{E-}02 * 32.04 = 3.37\text{E-}01$

System outputs

kg 1,2-dichloroethane in air = $2.08 * 0.2\% = 4.16\text{E-}03$

kg NH₃ in water = $(3.58\text{E-}03 * 0.05) - 7.16\text{E-}04 = 1.72\text{E-}02$

kg 1,2-dichloroethane in water = $(2.08 * 0.05) - 4.16\text{E-}03 = 9.98\text{E-}02$

kg NaOH in air = $1.68 * 0.2\% = 3.36\text{E-}03$

kg NH₃ in air = $3.58\text{E-}03 * 0.2\% = 7.16\text{E-}04$

kg NaOH in water = $(1.68 * 0.05) - 3.36\text{E-}03 = 8.07\text{E-}02$

kg CH₃OH in air = $3.37\text{E-}01 * 0.2\% = 6.73\text{E-}04$

kg CH₃OH in water = (3.37E-01 * 0.05) - 6.73E-04 = 1.62E-02

LCI improvement – Phase II

Completed the first stage of improvement, the second step concerned the introduction of energy usages in the synthesis of the four substances. As described in the manuscript, a combination of the Finechem tool and information already published in literature was used to fill the data lack. A detailed description of the tool developed by ETH was already published. For more details please consult literature.^{12,49} In order to run Finechem, all the procedure reported on <http://www.sust-chem.ethz.ch/tools/finechem> was followed. First the R project for statistical computing was downloaded. Then, in order to run the analysis, was necessary completed the information requested by the bullet points for each chemical. This operation has been facilitated through the use of the detailed information listed as a support of the previous literature.¹² In the case of NMP, as well as for all the other chemicals, the data used are depicted below in Table S2. After the analysis, the tool provides results in terms of CED, GWP and Ecoindicator 99. In order to simulate the energy requirements for NMP the CED value and its uncertainty were taken into account. As suggested by literature,⁵¹ the contribution of energy consumption involved in the upstream processes (raw material extraction and substance production) for the sector of organic chemical is around 57% of the total CED value. Therefore, the value predicted by Finechem was multiplied for 57% and then split using an average energy mix of European chemical plant⁴⁶ (Table S3). In the case of 1kg of N-methylpiperazine the following calculations should be considered:

CED estimation by Finechem - MJ eq. = 193.8 ±65.6

Average energy consumption in the manufacturing - MJ eq. = 193.8 * 0.57 = 110.4

50% Natural gas - MJ eq. = 110.4 * 0.5 = 55.2

38% Steam - MJ eq. = 110.4 * 0.38 = 42.0

12% Electricity - MJ eq. = 110.4 * 0.12 = 13.3

Life cycle impact assessment

After the completion of the LCI improvement stage, two different scenarios were created using SimaPro software: the first, which only includes the mass flows involved in the NMP synthesis and the second, which simulates the entire process filled with the energy requirements. Then, each of them was analyzed separately in order to show the improvements in terms of results achieved per method considered (CED and IPCC 2013), as reported in the manuscript (Figure 6).

Substance	Production Process	Process Input	Amount (kg)	Process Output	Released in air (kg)	Released in water (kg)
TBA	from olefin hydration ⁱ	Butene, mixed, at plant/RER U	7.97E-01	Butene	1.59E-03	3.82E-02
		Water, decarbonised, at plant/RER U	2.56E-01	-	-	-
NMP	from piperazine and methanol ⁱⁱ	Ethylene dichloride, at plant/RER U	2.08E+00	Ethane, 1,2-dichloro-	4.16E-03	9.98E-02
		Ammonia, steam reforming, liquid, at plant/RER U	3.58E-01	Ammonia	7.16E-04	1.72E-02
		Sodium hydroxide, 50% in H ₂ O, production mix, at plant/RER U	7.16E-01	Sodium hydroxide	1.43E-03	3.44E-02
		Methanol, at plant/GLO U	3.37E-01	Methanol	6.73E-04	1.62E-02
PRD	from aldehydes with ammonia ⁱⁱⁱ	Acetaldehyde, at plant/RER U	1.17E+00	Acetaldehyde	2.34E-03	5.63E-02
		Formaldehyde, production mix, at plant/RER U	4.00E-01	Formaldehyde	7.99E-04	1.92E-02
		Ammonia, liquid, at regional storehouse/RER U	2.27E-01	Ammonia	4.53E-04	1.09E-02
EBA	from salicylic acid with ethyl-sulfate ^{iv}	Ethanol from ethylene, at plant/RER U	8.76E-01	Ethanol	1.75E-03	4.20E-02
		Sulphur dioxide, liquid, at plant/RER U	4.06E-01	Sulfur dioxide	8.12E-04	1.95E-02
		Chlorine, liquid, production mix, at plant/RER U	4.49E-01	Chlorine	8.98E-04	2.16E-02
		Thionyl chloride *, **	7.54E-01	Thionyl chloride	1.51E-03	3.62E-02
		Phenol, at plant/RER U	5.96E-01	Phenol	1.19E-03	2.86E-02
		Sodium hydroxide, 50% in H ₂ O, production mix, at plant/RER U	5.06E-01	Sodium hydroxide	1.01E-03	2.43E-01
		Carbon dioxide liquid, at plant/RER U ***	2.79E-01	Carbon dioxide	1.39E-02	-
		Hydrochloric acid, from the reaction of hydrogen with chlorine, at plant/RER U	2.31E-01	Hydrogen chloride	4.62E-04	1.11E-02

Tab. S1 LCI - Mass flows involved in the production of chemicals, referred to the production of 1kg of each substance

ⁱ H.-D. Hahn, G. Dämbkes, N. Rupprich, H. Bahl H., *Butanols*, Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2010, DOI: 10.1002/14356007.a04_463.pub2.

ⁱⁱ S. Sridhar, R.G. Carter, *Diamines and Higher Amines, Aliphatic*, Kirk-Othmer Encyclopedia of Chemical Technology. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2001, DOI: 10.1002/0471238961.0409011303011820.a01.pub2; *US Pat.*, 4 727 143, 1988.

ⁱⁱⁱ S. Shimizu, N. Watanabe, T. Kataoka, T. Shoji, N. Abe, S. Morishita, H. Ichimura *Pyridine and Pyridine Derivatives*, Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2000, DOI: 10.1002/14356007.a22_399.

^{iv} SciFinder® - The choice for chemistry research™ <https://scifinder.cas.org> (accessed February 2015); M. R. Thomas, *Salicylic Acid and Related Compounds*, Kirk-Othmer Encyclopedia of Chemical Technology. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2000, DOI: 10.1002/0471238961.1901120920081513.a01; W. B. McCormack, B. C. Lawes, *Sulfuric and Sulfurous Esters*, Kirk-Othmer Encyclopedia of Chemical Technology. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2000, DOI: 10.1002/0471238961.1921120613030315.a01.

* Process not included in Ecoinvent database. Modeled based on process reported in literature (W. B. McCormack, B. C. Lawes, *Sulfuric and Sulfurous Esters*, Kirk-Othmer Encyclopedia of Chemical Technology. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2000, DOI: 10.1002/0471238961.1921120613030315.a01.) and standard estimation method developed by Hischer et al. 2005: a process efficiency of 95% over the entire stoichiometric equation; 0.2% of input released as air emissions; the difference between unreacted input and air emission is released in water; average energy consumption (e.g. 2MJ in the form of steam and 0.333kWh of electricity).

** Just added as kg amount in the air and water emissions

*** Assumed that all unreacted is released in air.

	TBA	NMP	EBA	PRD
Chemical descriptors				
Molecular weight (g/mol)	74.12	100.16	166.17	79.10
Number of N atoms	0	2	0	1
Number of halogen atoms	0	0	0	0
Number of rings (both aromatic and aliphatic)	0	1	1	1
Number of tertiary and quaternary C atoms	1	0	1	0
Number of heteroatoms within the rings	0	2	0	1
Number of unique substituents on aromatic ring systems in the molecule	0	0	2	0
Number of functional groups	1	2	3	1
Number O atoms in carbonyl groups	0	0	0	0
Number O atoms except those in carbonyl groups	1	0	2	0
Results from FineChem				
CED (MJ eq./ kg)	104.8±17.5	193.8±65.6	205.4±93.6	147.1±61.8

Tab. S2 FineChem tool - input and output values

Ecoinvent process		TBA	NMP	EBA	PRD
Energy values (MJ)					
Average CED values - evaluated by Finechem	-	104.8	193.8	205.4	147.1
Average energy consumption in the manufacturing ⁱ	-	59.7	110.4	117.1	83.8
Energy mix considered in the production process ⁱⁱ	Heat, natural gas, at industrial furnace low-NO _x >100kW/RER U	29.9	55.2	58.5	41.9
	Electricity, production mix RER/RER U	22.7	42.0	44.5	31.9
	Heat, unspecific, in chemical plant/RER U	7.2	13.3	14.0	10.1

Tab. S3 LCI – Energy consumption involved in the production of chemicals, referred to the production of 1kg of each substance

ⁱ based on: G. Wernet, C. Mutel, S. Hellweg, K. Hungerbühler, *J. Ind. Ecol.*, 2011, **15**, 96-107.

ⁱⁱ based on: Gendorf, Umwelterklärung 2000, Industrial Park Werk Gendorf, Burgkirchen, 2000.

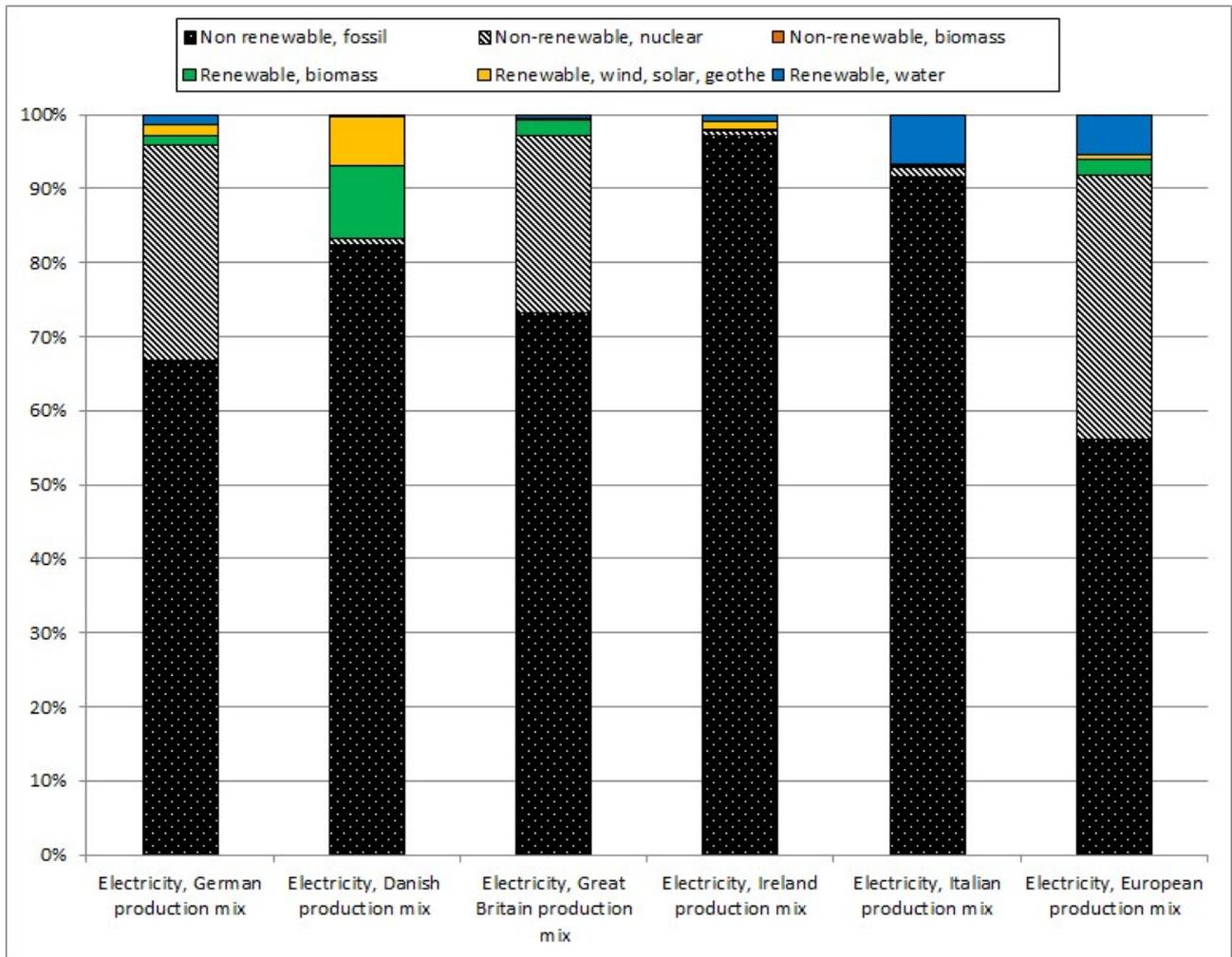


Fig. S1 Contribution analysis in terms of disaggregated CED values of the differences country energy mixes (1kWh)

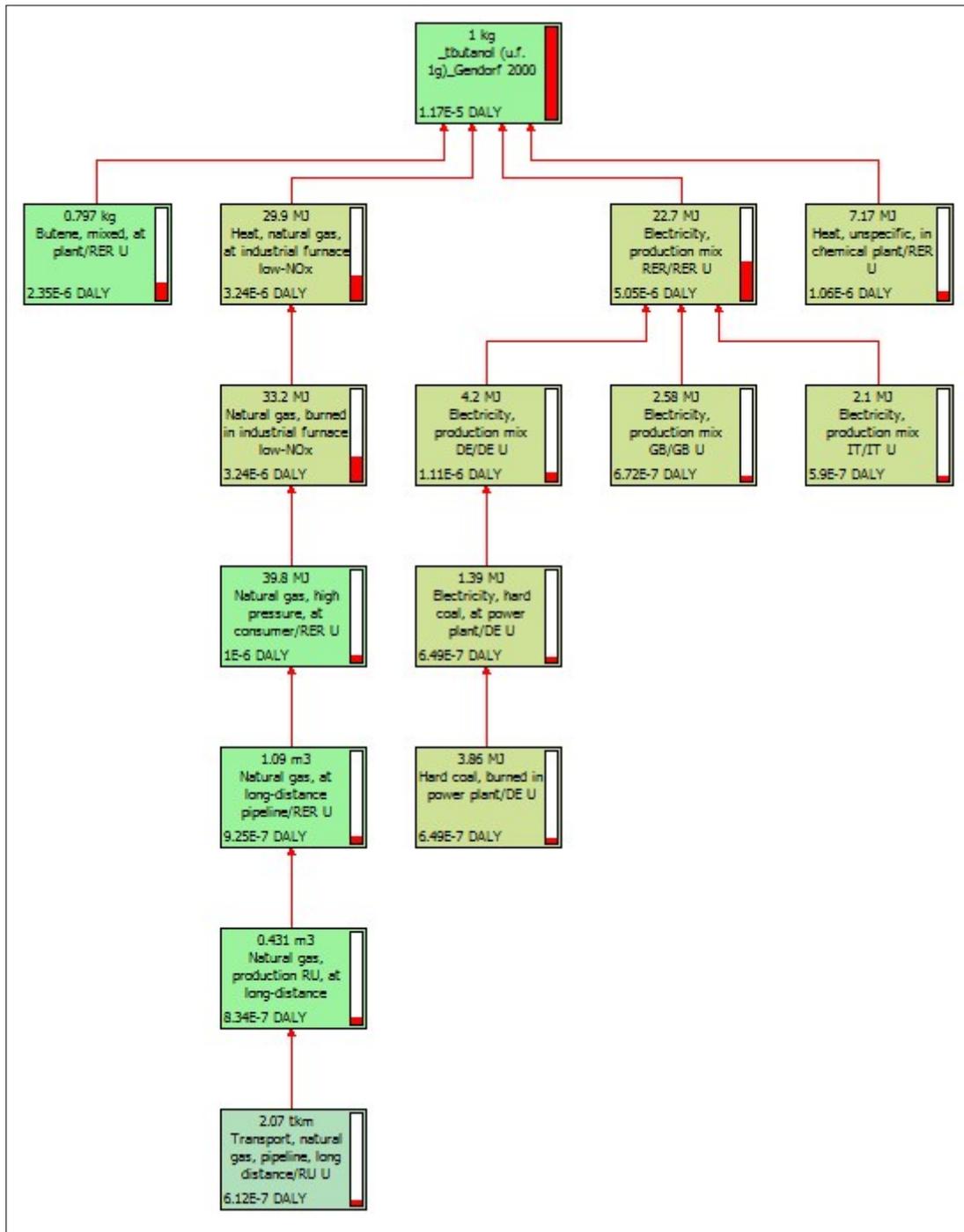


Fig. S2 Network tool results for TBA: processes with higher contribution for the HH category (5% cut-off).

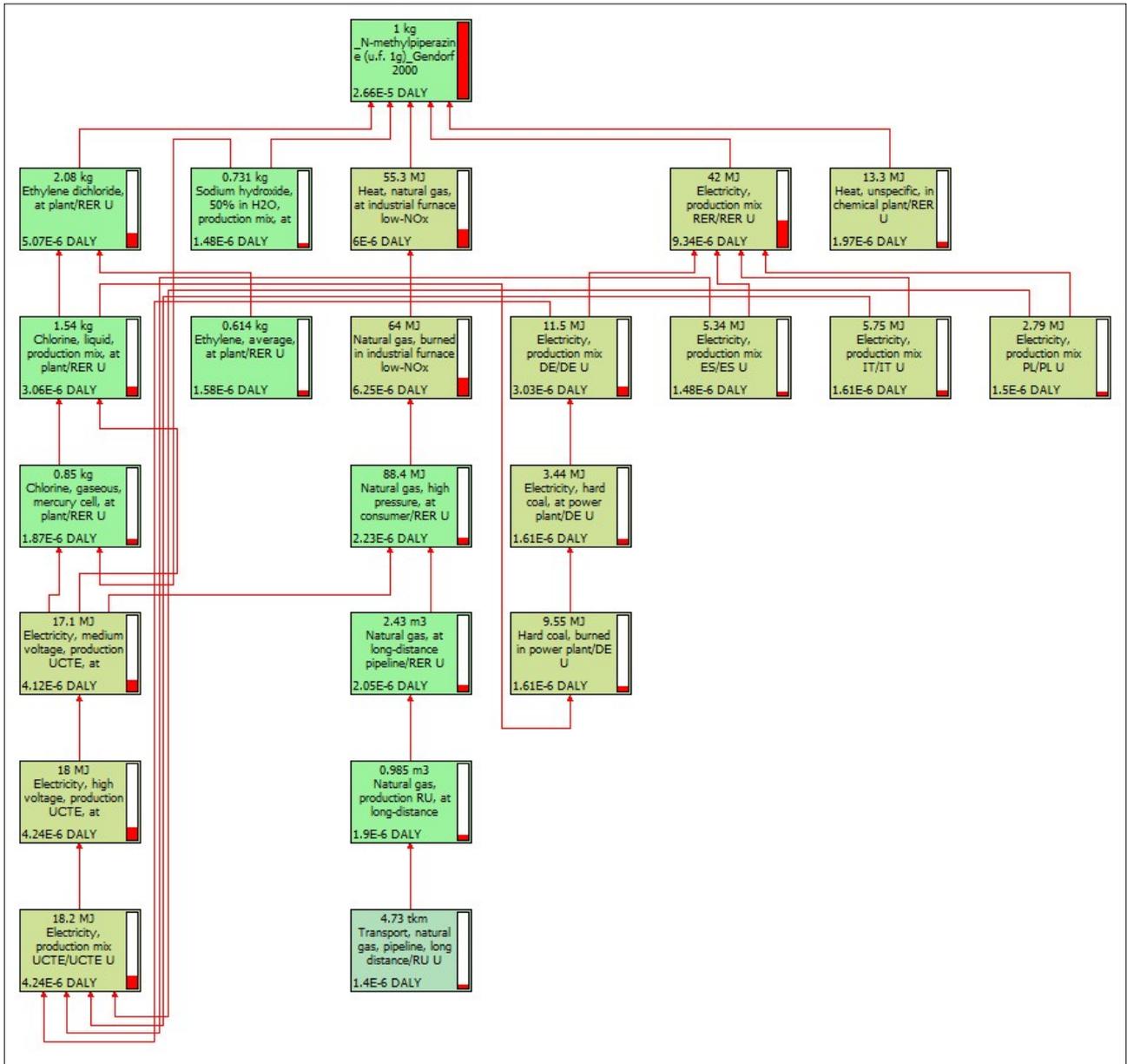


Fig. S3 Network tool results for NMP: processes with higher contribution for the HH category (5% cut-off).

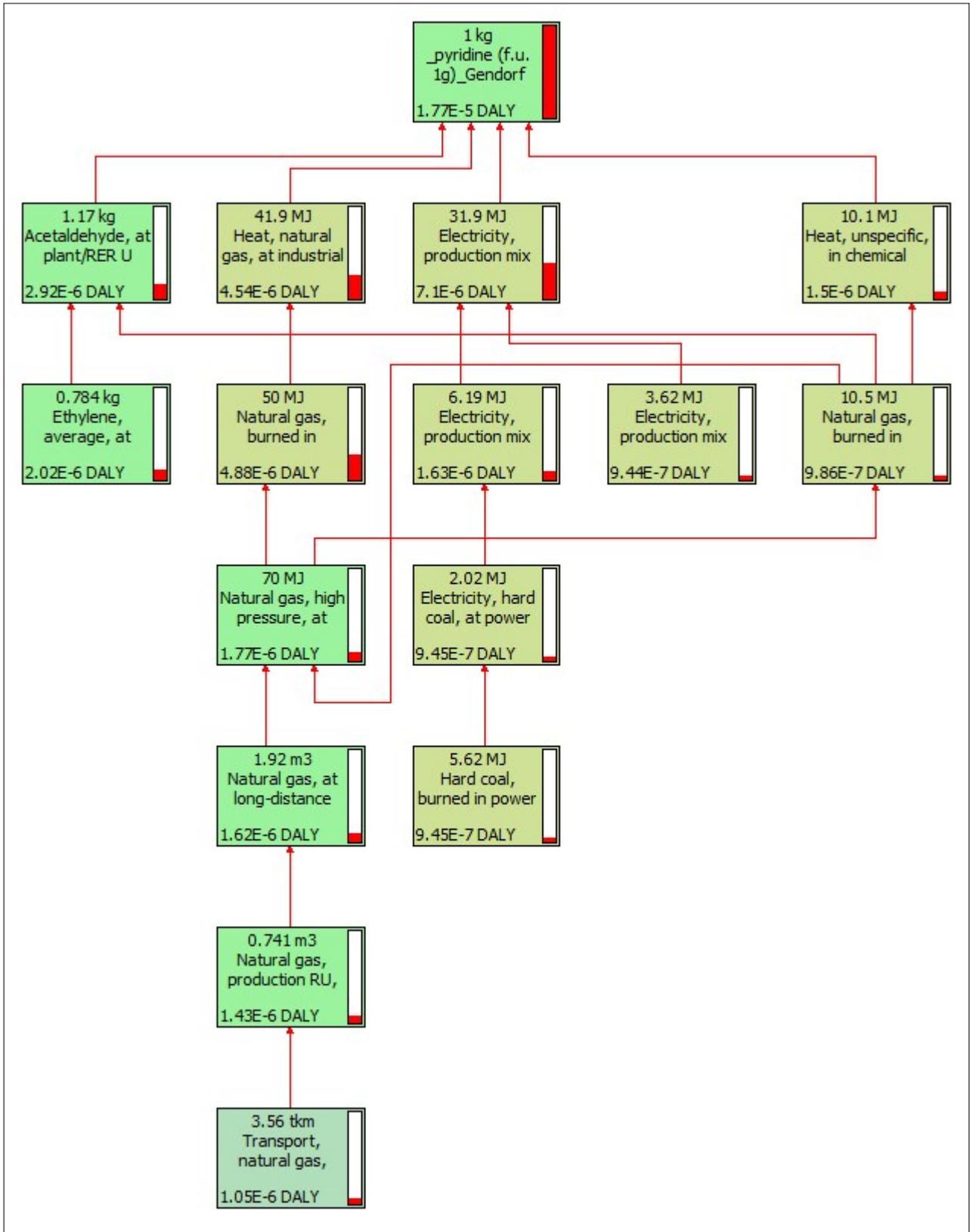


Fig. S4 Network tool results for PRD: processes with higher contribution for the HH category (5% cut-off).

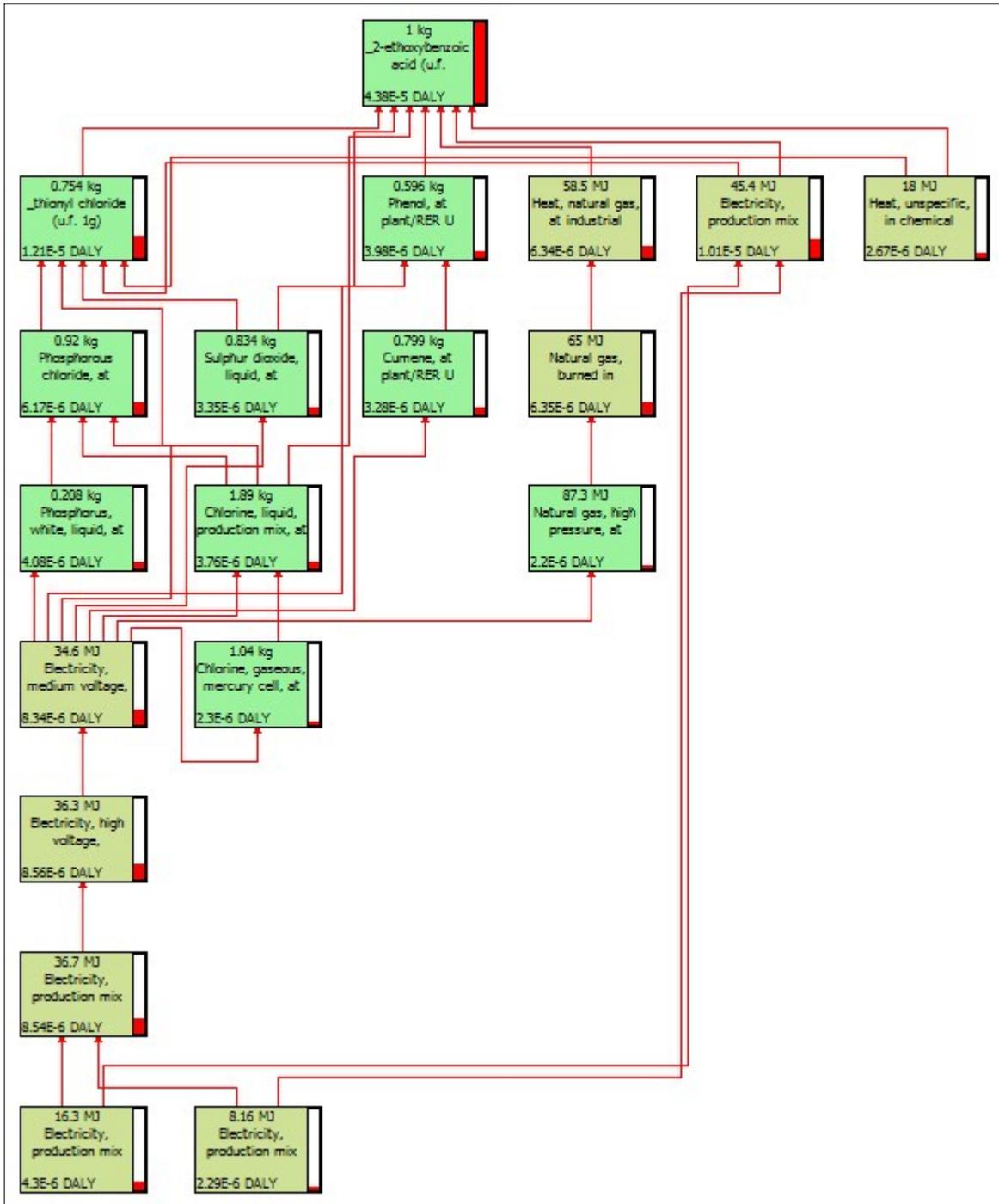


Fig. S5 Network tool results for EBA: processes with higher contribution for the HH category (5% cut-off).