ELECTRONIC SUPPLEMENTARY INFORMATION

Phytochemical compounds or their synthetic counterparts? A detailed comparison of the quantitative environmental assessment for the synthesis and extraction of Curcumin.

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APPENDIX A - EATOS software parameters

The green metrics, that software EATOS allows calculating, are expressed in details by the following equations 1-4.

$$MI = \frac{substrate(g) + solvent(g) + auxiliary\_materials(g) + catalyst(g) + \ldots}{product(g)} \quad (1)$$

$$E - factor = \frac{\sum waste(g)}{product(g)} \quad (2)$$

$$EI\_in = \frac{substrate(g) \cdot Q_{tot\_substrate} + solvent(g) \cdot Q_{tot\_solvent} + auxiliary\_materials(g) \cdot Q_{tot\_aux.mater.} + catalyst(g) \cdot Q_{tot\_catalyst} + \ldots}{product(g) \cdot Q_{tot\_product}}$$

(3)

$$EI\_out = \frac{\sum waste(g) \cdot Q_{tot\_waste}}{product(g) \cdot Q_{tot\_product}} \quad (4)$$

The total weighting factor Q_{tot} of each substance of the inward as well as of the outward materials flow represents the mean value calculated among the substance specific weighting factors Qi, according to equation 5. The index i accounts for the i^{th} weighting category among those which can be considered by EATOS: claiming of resources, risk, human toxicity, chronic toxicity, ecotoxicology, ozone creation, air pollution, accumulation, degradability, greenhouse effect, ozone depletion, nitrification, and acidification.

Each Qi assumes values comprised between 1 and 10, on the basis of a classifications made by the software itself, which depends on the specific characteristics of the substance considered.

$$Q_{tot} = \frac{\sum_{i=1}^{i=n} Q_i}{n} \tag{5}$$

The EATOS function *weighting of weighting* allows selecting the weighting categories to be considered in the study both for the input and for the output materials flow. Particularly, as concern the input materials the EATOS software allows selecting only the weighting categories claiming of resources and risk, while in the case of the output materials, all the remaining weighting categories can be selected.

In the present study both the two weighting categories claiming of resources and risk were considered in the weighting of input materials flow.

In the case of output materials flow the weighting categories considered were limited to those for which the corresponding values for at least one substance were available in the materials safety data sheet (MSDS), particularly those selected were human toxicity, chronic toxicity, ecotoxicology, ozone creation, accumulation, degradability and greenhouse effect. Moreover, the possibility of Q_i=0 assignment was considered in this work.

APPENDIX B - The indicator "Human health anticancer benefit cachexia"

A new indicator named "Human health anticancer benefit cachexia" was developed in order to include in the Life Cycle Assessment performed also one of the human health benefits of curcumin molecule, i.e. its curative effects on cachexia.

In order to quantify and characterize this new indicator, literature data were employed. Indeed it is reported[1] that neoplastic cachexia disappears in colorectal cancer (CRC) affected patients, with a daily administration of 0.36 g of curcumin for at least 30 days. Another study by Laviano et al.[2] pointed out a life period of 43 weeks as the average one for CRC affected patients which do not manifest cachexia. The same study highlighted that a weight loss >10% associated to the occurrence of cachexia syndrome significantly decreases the average survival period to 20 weeks.

Thus, on the basis of these studies, the characterization factor of the new indicator was calculated. Particularly it corresponds to the ratio between the gained lifetime and the annual amount of curcumin responsible for that benefit, as reported in equation 6

$$Characterization\_Factor = -\frac{(43-20)weeks}{0.36\cdot 10^{-3}\,\frac{kg}{day}\cdot 365days} = -175.04\,\frac{weeks}{kg}. \qquad (6)$$

The negative mark accounts for the net environmental benefit in the LCA framework, due to the curative effect of curcumin on cachexia.

The corresponding damage assessment factor expressed in DALY (Disability Adjusted Life Year), is represented by the ratio between the gained life time (expressed in years) and the European population (equation 7). For the latter, the value considered by the evaluation method employed (i.e. IMPACT 2002+) is 431 millions inhabitants, which is referred to the sole western Europe.

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[1] Z.Y. He, C.B. Shi, H. Wen, F.L. Li, B.L. Wang, Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin, *Cancer Invest J*, 2011, **29**, 208-213.

[2] A. Laviano, M.M. Meguid, A. Inui, M. Muscaritoli, F. Rossi-Fanelli, Therapy insight: cancer anorexia-cachexia syndrome-when all you can eat is yourself, *Nature Clinical Practice Oncol*, 2005, **2**, 158-165.

$$Damage\_Assessment\_Factor = \frac{-175.04\,\frac{weeks}{year}}{52\,\frac{weeks}{year}} \cdot \frac{1}{431 \cdot 10^{6}\, inhabitants} = -7.8101 \cdot 10^{-9}\,\frac{DALY}{kg}.$$

(7)

Normalisation operation needs to be performed in order to refer the previously reported damage assessment factor to a typical drug employed in the conventional treatment of colorectal cancer, i.e. Cetuximab, whose weekly therapy dose is $2.5 \cdot 10^{-4}$ kg/m^2.[3]

As reported in equation 8, describing the normalisation factor, this latter amount is referred to one year therapy, then multiplied for the average adult body surface area (BSA) value of 1.8 m^2,[4] and finally for the incidence of CRC.[5]

$$Normalisation\_factor = \frac{1DALY}{2.5 \cdot 10^{-4}\,\frac{kg}{m^2} \cdot 52\,\frac{weeks}{year} \cdot 1.8m^2} \cdot \frac{165}{1 \cdot 10^{5}} = 0.070513\,\frac{DALY}{kg} = 14.1818\,\frac{kg}{DALY}$$

(8)

The weighting factor chosen for the newly developed indicator was equal to 1, similarly to all of the other indicators employed in the present study.

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[3] N.A. Reynolds, A.J. Wagstaff, Cetuximab: in the treatment of metastatic colorectal cancer, *Drugs*, 2004, **64**, 109-118.

[4] J.J. Batzel, F. Kappel, D. Schneditz, H.T. Tran, in *Cardiovascular and respiratory systems: modeling, analysis, and control,* SIAM, Philadelphia, 2007, ch. 4, p. 168.

[5] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No.11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 18/12/2013.

TABLES

Table 1 ESI Detailed quantification of the different contributions to the EATOS metrics for the investigated synthesis of curcumin. As clearly visible the EATOS approach is limited to the mere chemicals employed.

Category	Substance	MI (kg of starting material/kg of product)	E (kg of waste/kg of product)	EI_in (PEI/kg)	EI_out (PEI/kg)
Sewage water	H_2O (out of HCl 0.5M solution)	53.8431	53.8431	26.9215	-
Auxiliary materials	Isolation (CH_3OH)*	8.9288	8.9288	40.1796	11.4799
	Reaction (HCl)	0.9898	0.9898	0.4949	0.2828
Solvent	N,N-dimethylformamide (DMF)	12.787	12.787	63.9352	29.2275
Impurities	out of acetylacetone	0.0023	0.0023	0.0034	0.0023
	out of B_2O_3	0.0094	0.0094	0.0567	0.0256
	out of DMF	0.0256	0.0256	0.1281	0.0586
	out of tributylborate	0.0579	0.0579	0.1158	0.0331
	out of *n*-butylamine	0.0050	0.0050	0.0176	0.0036
	out of HCl 0.5M	0.0011	0.0011	0.0005	0.0003
	out of methanol	0.0895	0.0895	0.4026	0.1150
catalysts	Tributyl borate	5.7309	5.7309	11.4618	3.2748
	n-butylamine	0.4972	0.4972	1.7401	0.3551
Substrates	Acetylacetone	0.4530	-	0.6794	-
	B_2O_3	0.4725	0.3150	2.8347	0.8549
	vanillin	1.8586	0.4819	3.7172	0.2753
By-products	unknown	-	0.7949	-	0.6668
Coupled products	B_2O_3	-	0.0945	-	0.2565
	H_2O	-	0.0978	-	-
Product	Curcumin	-	1	-	1
TOTAL		85.7517	85.7517	152.6891	47.9121

* a recyclable percentage of 80% was considered.

Table 2 ESI Life Cycle Impact Assessment (LCIA) midpoint results of the analyses carried out for 1kg of curcumin obtained with the three different strategies considered: synthesis, conventional Soxhlet extraction (CE) and microwave assisted extraction (MAE).

Impact category	Unit	Synthesis	CE	MAE
Carcinogens	kg C_2H_3Cl eq	2.08E+02	4.84E+03	1.03E+03
Non-carcinogens	kg C_2H_3Cl eq	2.10E+02	3.35E+03	1.06E+03
Respiratory inorganics	kg PM2.5 eq	8.43E+00	3.17E+02	7.25E+01
Ionizing radiation	Bq C-14 eq	1.22E+05	3.58E+06	1.35E+06
Ozone layer depletion	kg CFC-11 eq	1.27E-03	5.59E-02	2.04E-02
Respiratory organics	kg C_2H_4 eq	3.25E+00	1.29E+02	6.17E+01
Aquatic ecotoxicity	kg TEG water	1.09E+06	6.29E+07	8.42E+07
Terrestrial ecotoxicity	kg TEG soil	1.81E+05	8.20E+06	1.68E+06
Terrestrial acid/nitri	kg SO_2 eq	1.47E+02	6.02E+03	1.52E+03
Land occupation	m^2org.arable	-2.74E+01	-5.42E+03	1.30E+03
Aquatic acidification	kg SO_2 eq	4.51E+01	1.87E+03	4.11E+02
Aquatic eutrophication	kg PO_4 P-lim	1.79E+00	6.86E+01	2.84E+01
Global warming	kg CO_2 eq	1.71E+04	4.61E+05	1.04E+05
Non-renewable energy	MJ primary	1.70E+05	7.37E+06	2.17E+06
Mineral extraction	MJ surplus	4.98E+02	2.23E+04	2.18E+04
Renewable energy	MJ	1.49E+04	5.88E+05	1.05E+05

Table 3 ESI Life Cycle Impact Assessment (LCIA) end-point results of the analyses carried out for 1kg of curcumin obtained with the three different investigated strategies: synthesis, conventional Soxhlet extraction (CE) and microwave assisted extraction (MAE).

Damage category	**Unit**	**Synthesis**	**CE**	**MAE**
Human health	DALY	7,10E-03	2.46E-01	5.70E-02
Ecosystem quality	PDF*m2*yr	1,61E+03	6.84E+04	2.05E+04
Climate change	kg CO_2 eq	1,71E+04	4.61E+05	1.04E+05
Resources	MJ primary	1,70E+05	7.39E+06	2.19E+06
Renewable energy	MJ	1,49E+04	5.88E+05	1.05E+05