Supplementary Information

Risk and Life Cycle Assessment of Nanoparticles for Medical Applications Prepared Using Safe- and Benign-by-Design Gas-Phase Syntheses

P. Weyell[a], H.-D. Kurland[b], T. Hülser[c], J. Grabow[b], F. A. Müller[b] and D. Kralisch[a]*

a Friedrich Schiller University Jena, Pharmaceutical Technology and Biopharmacy, Lessingstraße 8, 07743 Jena, Germany. *Email: dana.kralisch@uni-jena.de; Fax: +49 3641 949942; Phone: +49 3641 949951
b Friedrich Schiller University Jena, Otto Schott Institute of Materials Research (OSIM), Löbdergraben 32, 07743 Jena, Germany.
c Institute of Energy and Environmental Technology e.V. (IUTA), Bliersheimer Straße 58-60, 47229 Duisburg, Germany.

Table 1: Results of XRF-Analysis of the (Co)LAVA nanopowders.

Nanoparticles	**XRF-Analysis**	
	Compound/Element	**Mass%**
SiliFe	SiO_2	63.30
	Fe_2O_3	36.29
	K	0.28
	Mn	0.06
	S	0.06
	Ni	0.01
	Zn	85 ppm
	S	0.02
γ-Fe_2O_3	Fe_2O_3	99.69
	Mn	0.18
	S	0.05
	Ni	0.02
	Zn	0.03
	Si	0.03

Table 2: Life Cycle Inventory – Pharmaceutical manufacturing

Ecoinvent v3.2 datasets	Input		Output	
Transport and logistic				
Market for petrol, unleaded [RER]	Petrol	2.13 g[a]	1 unit[b]	Pharma manufacturing (1 kg product)
Maintenance, lorry 28 metric ton [CH]	Maintenance lorry	$7.69\cdot10^{-7}$ unit[c]	Emissions	
Market for lorry, 28 metric ton [GLO]	Lorry	$7.69\cdot10^{-7}$ unit[c]	0.98 kg	Carbon dioxide
Packaging			$9.95\cdot10^{-4}$ kg	Nitrogen oxides
Offset printing, per kg printed paper [CH]	Paper	0.33 kg[d]	$1.87\cdot10^{-4}$ kg	Sulfur dioxide
Market for packaging glass, white [GLO]	Packaging glass, white	0.36 kg[d]		
Carton board box production service, with offset printing [CH]	Carton box	0.33 kg[d]		
Sterilisation				
Market for water, deionised, from tap water, at user [GLO]	Water	$1.16\cdot10^{-3}$ kg[e]		
Market for steel, chromiumsteel 18/8 [GLO]	Steel	$1.12\cdot10^{-6}$ kg[e]		
Pharmaceutical factory, construction of facilities				
Chemical factory construction, organics [RER]	Pharmaceutical factory	$5.49\cdot10^{-10}$ unit[f]		
Energy consumption				
Natural gas production [DE]	Natural gas	0.21 m³		
Market for light fuel oil [Europe without Switzerland]	Fuel oil	6.25 g		
Market for electricity, medium voltage [DE]	Electricity	1.66 kWh		

[a] 27.7 L petrol / 100 km, average density 0.75 kg/L, 14 lorries, 13341 km per lorry per year [1]

[b] 1 unit = 18200 t product per year

[c] 14 units[2]

[d] Representative data for primary and secondary packaging material, e.g. filling of Gadovist® in vials, printed patient information's, product transport in carton boxes.

[e] Sterilisation of 2618 t product per year, 15 L water / 540 kg product, autoclave 700 kg / life time 10 years

[f] 1 unit = 1 factory with life time of 100 years

[1] KBA (the Federal Bureau of Motor Vehicles and Drivers), 2016.

[2] https://www.lichteindruck.de/projekte/teva-ratiopharm/ (accessed 16th October 2017)

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Table 3: Pedigree data quality matrix[3].

	Indicator score	1	2	3	4	5
A	**Reliability of the source**	Verified data based on measurements	Verified data partly assumptions or non-verified data based on measurements	Non-verified data partly based on assumptions	Qualified expert estimation	Non-qualified estimate or unknown origin
B	**Completeness**	Representative data from a sufficient sample of sites over an adequate period to even out normal fluctuations	Representative data from a smaller number of sites but for adequate periods	Representative data from an adequate number of sites but from shorter periods	Representative data from a smaller number of sites and shorter periods or incomplete data from an adequate number of sites and periods	Representativeness unknown or incomplete data from a smaller number of sites and/or from shorter periods
C	**Temporal correlation**	Less than 3 years of difference to year of study	Less than 6 years of difference	Less than 10 years of difference	Less than 15 years of difference	Age of data unknown or more than 15 years of difference
D	**Geographical correlation**	Data from area under study	Average data from larger area in which the area under study is included	Data from area with similar production conditions	Data from area with slightly similar production conditions	Data from unknown area or area with different production conditions
E	**Further technological correlation**	Data from enterprises, processes and materials under study	Data from processes and materials under study but from different enterprises	Data from processes and materials under study but from different technology	Data on related processes or materials but from same technology	Unknown technology or data on related processes or materials, but from different technology

[3] B. P. Weidema, *The International Journal of Life Cycle Assessment*, 1998, 3, 259-265.

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Table 4: Data quality assessment for LCI models on manufacturing of SiliFe- and γ-Fe_2O_3 by laservaporisation in (Co)LAVA-process, flame spray pyrolysis (FSP) and synthesis of reference Gadovist® (Gd).

Data sets from Ecoinvent data base v 3.2; allocation cut-off (results) [CH] = Swiss, [DE] = German, [RER] = European, [GLOB] = global	**Model**	**A**	**B**	**C**	**D**	**E**
Anionic resin production [CH]	Gd	3	4	5	3	1
Argon production, liquid [RER]	(Co)LAVA	3	4	1	5	1
Cationic resin production [CH]	Gd	3	4	5	3	1
Carbon dioxide production, liquid [RER]	(Co)LAVA	3	2	5	3	2
Carton board box production service, with offset printing [CH]	FSP (Co)LAVA Gd	2	2	1	3	4
Chloroacetic acid production [RER]	Gd	3	2	1	2	1
Compressed air production, 800 kPa gauge, <30kW, average generation [RER]	FSP (Co)LAVA	3	5	1	2	3
Chromium steel pipe production [GLO]	FSP (Co)LAVA	5	4	1	2	2
Dichloromethane production [RER]	Gd	1	2	1	2	2
Diethyl ether production [GLO]	Gd	2	4	1	2	2
N,N-dimethylformamide production [RER]	Gd	2	4	1	2	1
Electricity, high voltage, production mix [DE]	(Co)LAVA	5	5	1	1	5
Ethyl acetate production [RER]	Gd	1	4	1	2	1
Glass tube production, borosilicate [DE]	(Co)LAVA	2	2	1	1	4
Heat pump production, 30kW [RER]	(Co)LAVA	4	4	1	2	4
Isopropanol production [RER]	FSP	3	4	1	2	1
Maintenance lorry 28 metric ton [CH]	FSP LAVA Gd	4	4	1	3	2
Market for acetone [GLO]	Gd	2	2	1	1	1
Market for acetonitrile [GLO]	Gd	2	2	1	2	2
Market for acetylene [GLO]	Gd	3	5	1	3	5
Market for benzaldehyde [GLO]	Gd	3	3	4	1	1
Market for chlorine, liquid [GLO]	(Co)LAVA	1	4	1	2	2
Market for chlorosulfonic acid [GLO]	Gd	2	2	4	2	4
Market for copper [GLO]	Gd	2	4	3	2	2
Market for dichloromethane [GLO]	Gd	3	4	5	2	2
Market for diethanolamine [GLO]	Gd	3	2	5	5	2
Market for dioxane [GLO]	Gd	3	2	4	2	2
Market for electricity, medium voltage [DE]	FSP (Co)LAVA Gd	1	1	3	1	5
Market for ethanol, without water, in 99.7% solution state, from fermentation, at service station [CH]	Gd	3	3	1	3	1
Market for ethylenediamine [GLO]	Gd	3	4	5	2	1
Market for ethylene carbonate [GLO]	Gd	2	3	1	2	2
Market for formaldehyde [GLO]	Gd	1	4	1	2	1
Market for helium [GLO]	(Co)LAVA	2	4	1	2	1
Market for hydrochloric acid, without water, in 30% solution state [RER]	Gd	2	2	1	2	2
Market for hydrogen, liquid [RER]	Gd	5	3	1	2	5

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(Table 4 continued)

Market for hydrogen peroxide, without water, in 50% solution state [GLO]	Gd	1	3	1	2	1
Market for iron (III) chloride, without water, in 40% solution state [GLO]	Gd	3	3	1	3	1
Market for iron scrap, sorted, pressed [GLO]	(Co)LAVA	3	4	1	2	2
Market for lead concentrate [GLO]	Gd	2	3	1	2	1
Market for light fuel oil [Europe without Switzerland]	FSP (Co)LAVA Gd	1	1	1	2	1
Market for lorry, 28 metric ton [GLO]	FSP (Co)LAVA Gd	5	5	1	2	5
Market for magnesium sulfate [GLO]	Gd	3	5	1	2	4
Market for methane, 96% by volume [GLO]	FSP	3	4	1	2	2
Market for N,N-dimethylformamide [GLO]	Gd	3	5	1	2	1
Market for nitrogen, liquid [RER]	FSP (Co)LAVA	1	1	1	2	1
Market for oxygen, liquid [RER]	FSP	3	1	1	2	5
Market for petrol, unleaded [RER]	FSP (Co)LAVA Gd	1	2	1	2	5
Market for pig iron [GLO]	FSP	4	5	1	2	1
Market for pyridine [GLO]	Gd	1	2	4	2	1
Market for samarium europium gadolinium concentrate, 94% rare earth oxide [GLO]	Gd	1	1	1	1	1
Market for selenium [GLO]	(Co)LAVA	3	1	1	5	1
Market for sodium hydroxide, without water, in 50% solution state [GLO]	(Co)LAVA Gd	1	1	1	2	2
Market for steel, chromium steel 18/8 [GLO]	FSP (Co)LAVA	4	5	1	2	5
Market for sulfur [GLO]	Gd	3	2	1	2	1
Market for sulfuric acid [GLO]	Gd	2	1	5	2	1
Market for transport, freight, lorry 16-32 metric ton, EURO4 [GLO]	FSP (Co)LAVA Gd	3	2	1	3	1
Market for water, deionized, from tap water, at user [CH]	FSP (Co)LAVA Gd	2	3	1	3	1
Market for zinc oxide [GLO]	(Co)LAVA	3	1	4	5	1
Market for zinc sulfide [GLO]	(Co)LAVA	3	1	4	5	1
Methanol production, from synthetic gas [CH]	Gd	1	4	1	3	3
Municipal waste incineration facility construction [CH]	FSP	2	4	1	3	3
Natural gas production [DE]	FSP (Co)LAVA Gd	1	3	5	1	1
Nitric acid production, product in 50% solution state [RER]	FSP Gd	1	1	5	2	1
Offset printing, per kg printed paper [CH]	FSP LAVA Gd	1	2	1	3	3

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(Table 4 continued)

Market for packaging glass production, white [GLO]	FSP LAVA Gd	2	5	1	1	4
Market for palladium [GLO]	Gd	1	2	1	3	3
Market for zinc concentrate [GLO]	Gd	1	3	1	3	2
Pig iron production [GLO]	FSP	3	1	1	2	1
Potassium hydroxide production [RER]	Gd	1	5	1	3	2
Process-specific burdens, hazardous waste incineration plant [CH]	FSP	1	3	1	3	2
Silicon carbide production [RER]	FSP	2	3	1	2	3
Silica sand production [DE]	(Co)LAVA Gd	2	4	1	1	3
Sodium ethoxide production [RER]	Gd	1	4	4	2	1
Steam production in chemical industry [RER]	FSP (Co)LAVA Gd	1	1	1	2	2
Sulfuric acid production [RER]	Gd	1	4	5	2	2
Toluene production, liquid [RER]	Gd	1	1	1	2	1
Treatment of hazardous waste, hazardous waste incineration [CH]	Gd	1	2	1	3	1
Trimethylamine production [RER]	Gd	3	4	5	2	4
Ventilation system production, decentralized, 6 x 120 m3/h, steel ducts [CH]	FSP (Co)LAVA	3	3	1	3	3
Water production, deionized, from tap water, at user [CH]	FSP (Co)LAVA Gd	2	3	1	3	1
User defined data sets						
Autoclave in pharmaceutical manufacturing	FSP (Co)LAVA Gd	1	4	2	1	1
Chemical manufacturing	FSP (Co)LAVA Gd	1	2	1	1	3
FSP	FSP	2	2	1	1	1
Hematite production	(Co)LAVA	3	4	5	1	3
Laser construction	(Co)LAVA	3	4	5	3	4
(Co)LAVA-process	(Co)LAVA	2	4	1	1	1
Production of iron (III)-nitrate	FSP	3	5	3	5	5
Pharmaceutical manufacturing	FSP (Co)LAVA Gd	1	2	2	1	4
Synthesis of cyclen as starting material for gadubutrol synthesis	Gd	1	4	5	5	1
Synthesis of gadubutrol	Gd	1	4	2	5	1

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Table 5: Modelling, references, Comments and assumptions in LCI of Gadovist®.

Modelling	Comments & Assumptions	References
Chemical manufacturing	Data set considered for modelling of chemical manufacturing for all synthesis steps German energy mix Chemical factory with a life time of 100 years, production rate of 1 675 800 t per year Input: Energy mix (natural gas, light fuel oil, heat by steam production, electricity) Output: Emissions to air (carbon dioxide, sulfur dioxide, nitrogen oxide), waste water pollutants (ammonium, chloride, nitrogen, sulfate)	Umwelterklärung 2017 – Chemiepark Gendorf.
Synthesis of gadobutrol (Gadovist®)		J. Platzek et al., *Inorganic Chemistry*, 1997, **36**, p. 6086
Synthesis of cyclen	Starting material in the synthesis of gadobutrol. Synthesis starts with tosylation of diethanolamine and diethylenetriamine followed by cyclisation.	T. J. Atkins et al., *Organic Syntheses*, 1978, **58**, p.86
Tosylation	Stoichiometric calculation. Reaction with para-toluene sulfonyl chloride.	Organikum, 23. Edition, Wiley VCH Verlag GmbH, Weinheim 2009, p. 664.
Synthesis of para-toluene sulfonyl chloride	Reaction of toluene with chlorosulfuric acid (molar ratio 1 : 3) at room temperature.	Organikum, 23. Edition, Wiley VCH Verlag GmbH, Weinheim 2009, p. 369.
Synthesis of MOCO*	Starting material in the synthesis of gadobutrol. Reaction of acetylene and formaldehyde to 2-butyn-1.4-diol of formaldehyde by use of a composite catalyst based on bismuth (III) oxide and copper (II) oxide. *Cis*-2-butene-1.4-diol is formed in hydrogenation by use of palladium as catalyst. A cyclic acetal is formed in reaction with acetone. Then, the π-bound is epoxidised in the presence of meta-chloroperbenzoic acid.	P. Pässler et al., Acetylene. Ullmann's Encyclopedia of Industrial Chemistry, 2008. Organikum, 23. Edition, Wiley VCH Verlag GmbH, Weinheim 2009, p. 476. N. Prileschajew, *Berichte der deutschen chemischen Gesellschaft*, 1909, **42**, p. 4811.

(Table 5 continued)

Synthesis of *cis*-2-butene-1.4-diol		P. Pässler et al., *Acetylene*, Ullmann's Encyclopedia of Industrial Chemistry, 2008. W. Reppe et al., *European Journal of Organic Chemistry*, 1955, **596**, p. 6 H. Gräfje et al., *Butanediols, Butenediol, and Butynediol,* Ullmann's Encyclopedia of Industrial Chemistry, 2000.
Composite catalyst of bismuth (III) oxide and copper (II) oxide	The production of 2-butyn-1.4-diol can be carried out continuously in a reactor cascade (3-5 reactor systems). The catalyst is implemented in a fixed bed of coated strains (diameter 4 mm, length 10 mm, volume 125.7 mm³ per strain). 3 strains were assumed in each of five reactor systems with an overall volume of 1885.5 mm³. Bismuth (III) oxide and copper (II) oxide will obtained by reaction of the respective metal nitrates (stoichiometric calculation). A dataset of the resource extraction of copper is integrated in Ecoinvent database v3.2. Bismuth is a byproduct in, e.g. lead extraction. An average value of 1000 g Bi / t Pb was considered.	H. Gräfje et al., *Butanediols, Butenediol, and Butynediol,* Ullmann's Encyclopedia of Industrial Chemistry, 2000. W. Reppe et al., *European Journal of Organic Chemistry*, 1955, **596**, p. 6 H. W. Richardson, *Copper Compounds*, Ullmann's Encyclopedia of Industrial Chemistry, 2000. A. F. Holleman, E. Wiberg, N. Wiberg, *Lehrbuch der Anorganischen Chemie*, 102. Auflage. Walter de Gruyter & Co, Berlin 2007, p. 827. J. Krüger et al., *Bismuth, Bismuth Alloys, and Bismuth Compounds*, Ullmann's Encyclopedia of Industrial Chemistry, 2003.
Palladium catalyst		Palladium catalyst, US 5063194 A. BASF, 1991.
Synthesis of meta-chloro-peroxybenzoic acid	Benzoyl chloride is formed in chlorination of benzaldehyde. Further functionalization to meta-chlorobenzoyl chloride in Friedel-Crafts reaction. meta-chloroperbenzoic acid is formed in reaction with hydrogen peroxide.	Wöhler and Liebig, *Annalen der Pharmacie*, 1832, **3**, p. 249. EP0001252 A1. Europäische Patentschrift, 1979. *Organic Syntheses*, 1988, **6**, p.276; *Organic Syntheses*, 1970, **50**, p.15.

*4,4-dimethyl-3.5.8-trioxabicyclo[5.1.0]octane

Occupational safety assessment – Stoffenmanager Nano

Hazard characterisation of SiliFe nanoparticles

Material characterisation: Superparamagnetic SiliFe composite nanoparticles are characterised by a maghemite inclusion in a spherical matrix of amorphous silicon dioxide. The surface chemistry and interaction of the nanoparticles are similar to amorphous silicon dioxide nanoparticles as long as the silica matrix is closed.

Assessment Approach: Evaluation of hazard data of silica nanoparticles as analogous material.

Hazard data: OECD Safety Data Sheet on silica nanoparticles[4]. Amorphous silicon dioxide nanoparticles NM 200 - NM 204 in OECD testing program.

Table 6: Toxicity evaluation of silica nanoparticles.

	NM 200	NM 201	NM 202	NM 203	NM 204	Methods	Hazard group allocation	Limits by ISO TG 12901-2
Acute toxicity - inhalation -	No signs of toxicity	No signs of toxicity	No signs of toxicity	No signs of toxicity	-	OECD TG 403	A	> 5 mg/L
Acute toxicity - oral -	LD50 (rat) > 2000 mg/kg bw	LD50 (rat) > 2000 mg/kg bw	LD50 (rat) > 3300 mg/kg bw	LD50 (rat) > 3300 mg/kg bw	LD50 (rat) > 2000 mg/kg bw	OECD TG 401	A	> 2000 mg/kg bw
Acute toxicity - dermal -	LD50 (rabbit) > 5000 mg/kg bw	LD50 (rabbit) > 5000 mg/kg bw	-	-	LD50 (rabbit) > 5000 mg/kg bw	Draize Test	A	> 2000 mg/kg bw
Skin irritation	No signs of irritation	No signs of irritation	No signs of irritation	No signs of irritation	No signs of irritation	OECD TG 404	A	No or low signs of toxicity
Eye irritation	No signs of irritation	No signs of irritation	No signs of irritation	No signs of irritation	Weakly irritation, reversible after 72 h	Draize Test	A	No or low signs of toxicity
Mutagenicity	No signs of toxicity	No signs of toxicity	No signs of toxicity	No signs of toxicity	-	OECD TG 471, 473, 474,476	A	No signs of toxicity
Cancerogenity	Negative*					OECD TG 453		No signs of toxicity
Reproductive toxicity	No signs of toxicity	-	No signs of toxicity	No signs of toxicity	-	OECD TG 415, 416	A	No signs of toxicity

bw body weight

* Based on data of bulk substance

[4] *SILICON DIOXIDE: SUMMARY OF THE DOSSIER Series on the Safety of Manufactured Nanomaterials No. 71,* ENV/JM/MONO(2016)23, Organisation for Economic Cooperation and Development OECD, 2016.

Occupational safety assessment – Stoffenmanager Nano 1.0

Table 7: Description of the employees working conditions in Scenario A – D for evaluation of exposure score in occupational safety assessment using Stoffenmanager Nano.

	Scenario A	Scenario B	Scenario C	Scenario D
	Continuous manufacturing of nanoparticles in LAVA or FSP.	**Maintenance of process plant once a year (e.g. exchange of filter system) without use / with personal protective equipment (filter mask FPP2 or full-face powered air respirator TMP3).**	**Filling and packaging of the nanoparticles as sterile pharmaceutical product, change in potential exposure risk due to separate filling system (e.g. a glove box).**	**Transport and storage of the packaged final pharmaceutical product.**
Source domain	Release of primary particles during actual synthesis	Handling of bulk aggregated/agglomerated nanopowders	Spraying or dispersion of a ready-to-use nanoproduct	Spraying or dispersion of a ready-to-use nanoproduct
Product type			Intermediate	Ready-to-use nanoproduct
Product appearance	Powder	Powder	Liquid suspension	Liquid suspension
Dustiness	High	High	-	-
Moisture content	Dry product	Dry product	-	-
Viscosity of the liquid	-	-	Low (like water)	Low (like water)
Mass concentration in the product	100%	100%	2.5%[d]	2.5%[d]
Does the product contain fibers?	No	No	No	No
Inhalation hazard	Non hazardous	Non hazardous	Non hazardous	Non hazardous
Characterize your task	Flame pyrolysis[a]	Handling of products in small amounts (up to 100 g)	Handling of liquids using low pressure, low speed with large or medium quantities	Handling of (almost) undisturbed liquids (very low speed) very low quantities (under controlled conditions) of liquids in tightly closed containers
Duration task	4 to 8 hours a day[b]	2 to 4 hours	4 to 8 hours	4 to 8 hours a day
Frequency task	4 to 5 days a week[b]	1 day a month	4 to 5 days a week	4 to 5 days a week
Is the task carried out in the breathing zone of an employee (distance head-product < 1 m)?	No	Yes	Yes	No

(Table 7 continued)

	Scenario A	Scenario B	Scenario C	Scenario D
Is the working room being cleaned daily?	No	No	Yes	No
Are inspections and maintenance of machines/ancillary equipment being done at least monthly to ensure good condition and proper functioning and performance?	Yes	Yes	Yes	Yes
Volume of the working room?	< 100 m³	< 100 m³	< 100 m³	< 100 m³
Ventilation of the working room?	Mechanical and/or natural ventilation	Mechanical and/or natural ventilation	Mechanical and/or natural ventilation	Mechanical and/or natural ventilation
Local control measures?	Glove boxes/bags[c]	No	No control measures at the source[e]	No control measures at the source
	-	-	Glove boxes/bags[f]	-
Is the employee situated in a cabin?	The worker works in a cabin without a specific ventilation system (control room)	No	The worker does not work in a cabin	The worker does not work in a cabin
Is personal protective equipment applied?	None	None	None	None
		Filter mask FPP2	Filter mask FPP2	
		Full-face powered air respirator TMP3	Full-face powered air respirator TMP3	

[a] The term “flame pyrolysis” represents a gas phase manufacturing process.
(see in detail table 8 in Van Duuren Stuurman et al. *Ann. Occup. Hyg*. **2012**, *56*, 5, p. 525)

[b] Continuous manufacturing

[c] Completely enclosed manufacturing plant

[d] Suspension 25 mg/mL

[e] No separate enclosed filling system

[f] Separate enclosed filling system

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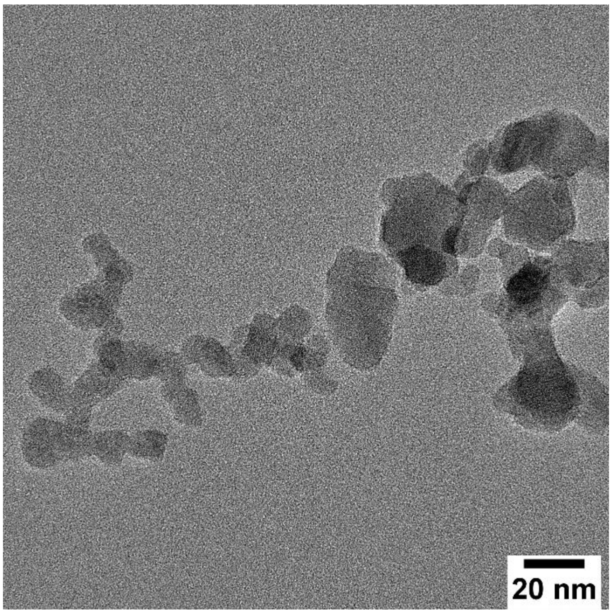

Figure 1: TEM image of iron oxide nanoparticles generated in a flame spray process on the pilot plant scale

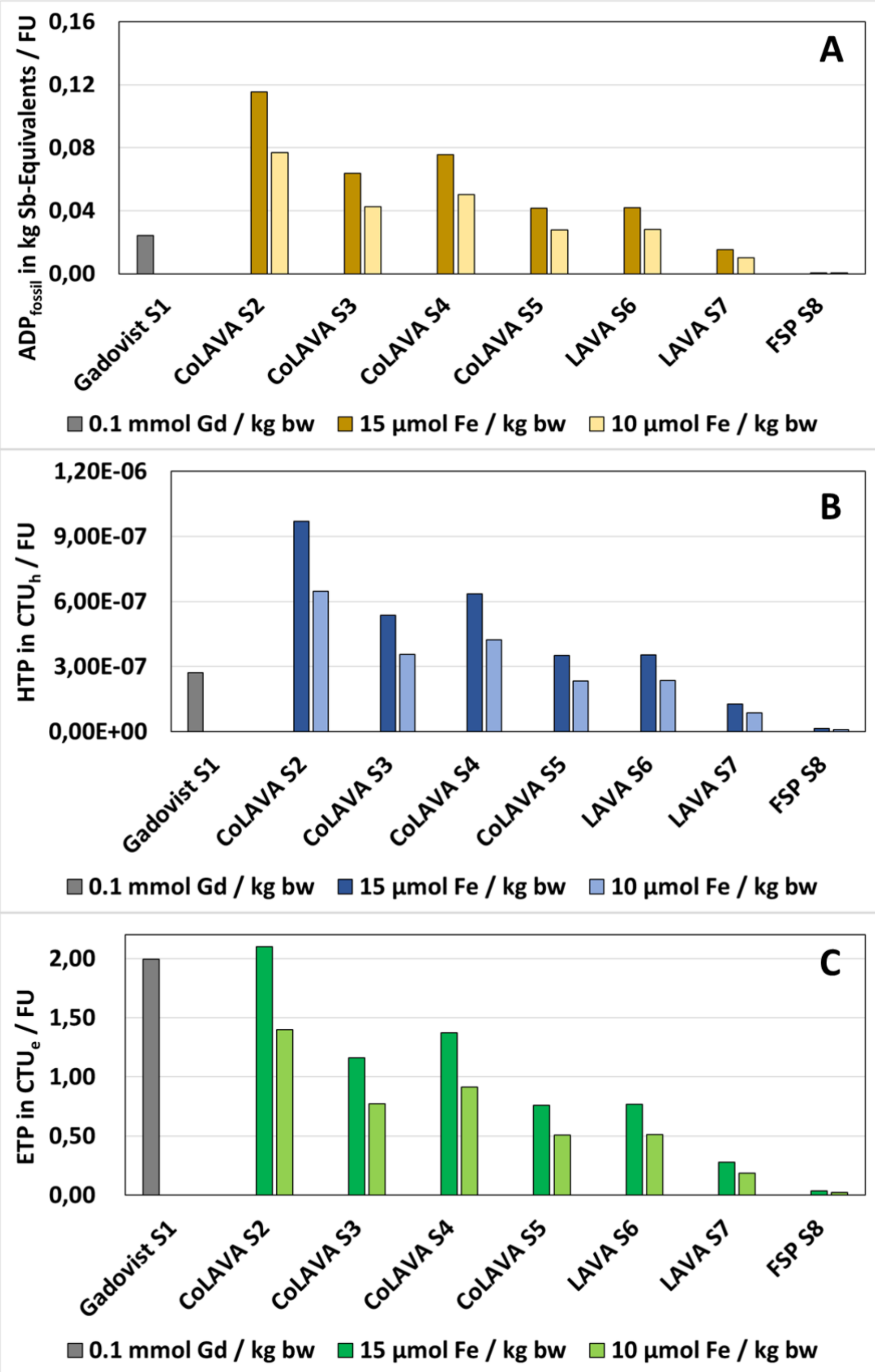

Figure 2: LCIA of SiliFe nanoparticle synthesis by CoLAVA-process, γ-Fe_2O_3 nanoparticles by LAVA-process and FSP as well as Gadobutrol (Gadovist®) as reference – Resource Depletion Potential of fossil fuels (A), Human Toxicity Potential (B) and Ecotoxicity Potential (C)

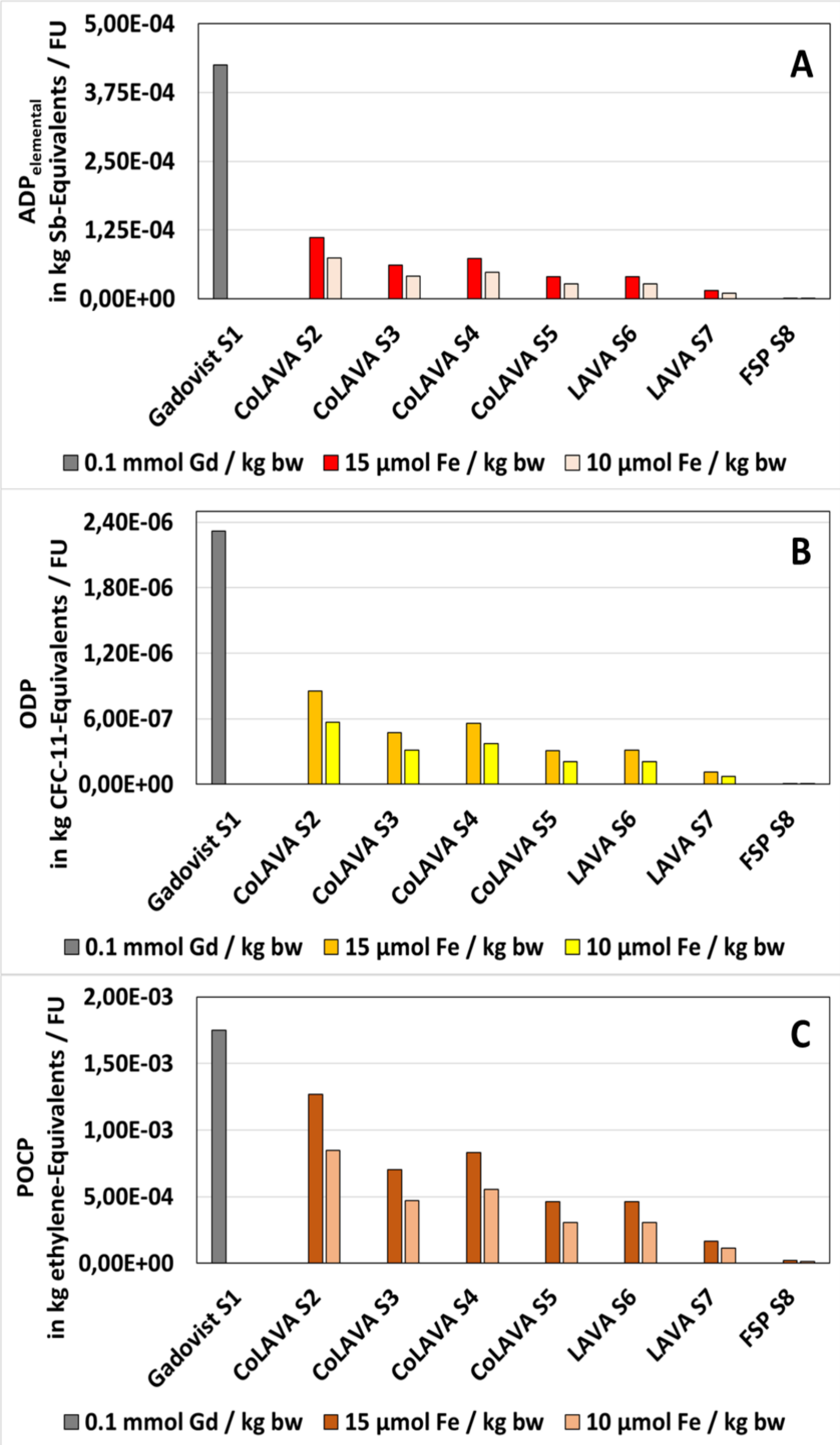

Figure 3: LCIA of SiliFe nanoparticle synthesis by CoLAVA-process, γ-Fe_2O_3 nanoparticles by LAVA-process and FSP as well as Gadobutrol (Gadovist®) as reference – Resource Depletion Potential of metals and minerals (A), Ozone Depletion Potential (B) and Photochemical Ozone Creation Potential (C).

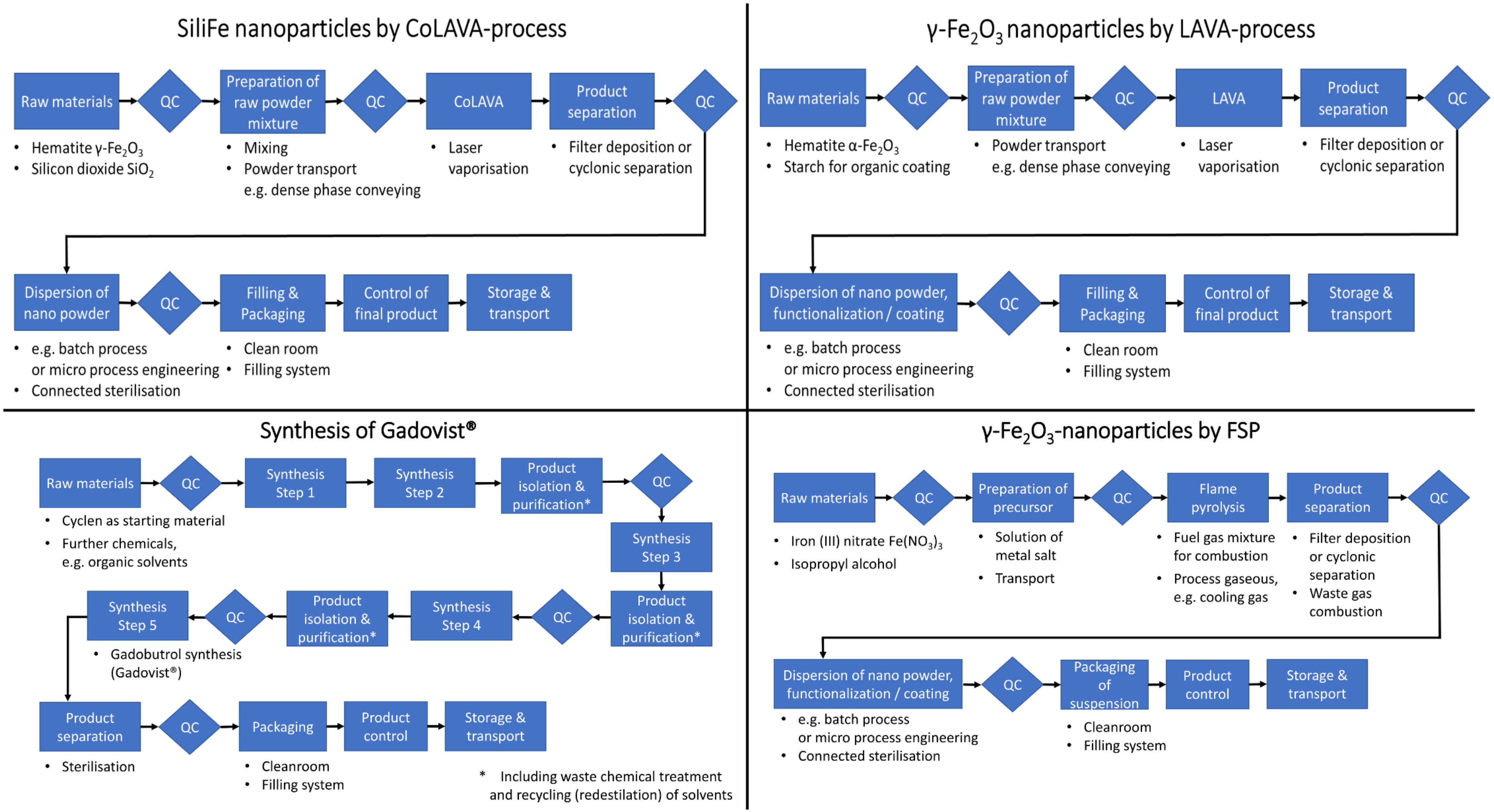

Figure 4: Process schemes for MRI diagnostic product containing SiliFe nanoparticle produced by CoLAVA-process, γ-Fe_2O_3 nanoparticles produced by LAVA-process or FSP, alternatively containing Gadobutrol (Gadovist®).