

HANDLING OF OEB-3 (practical example)

Ajinomoto OmniChem

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OmniChem at a Glance

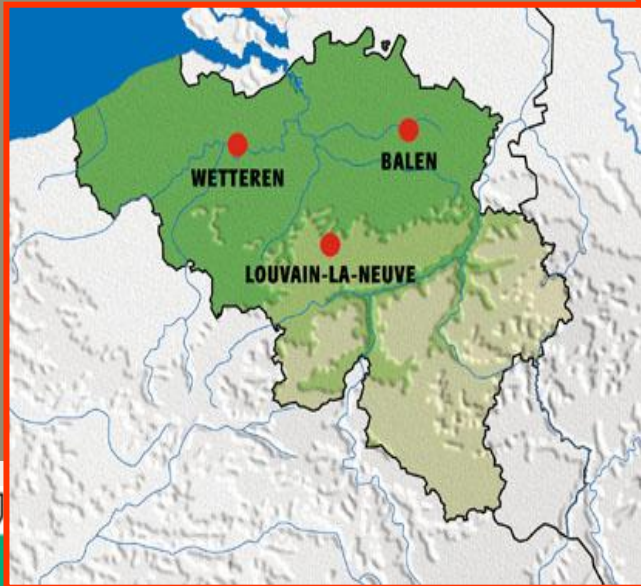
- CMO with 3 cGMP sites in Belgium, workforce: 700
- ICH Q7 compliant, cGMP certified & FDA approved since 1975
- Multi-purpose production (>600 m³ capacity)

- Reactor size : from 50 to 11,000 liters
- 1258MT of products of which 189 MT API produced in 2012
- Wide range of technologies

- HAPI expertise more than 30 years
- Frequent & significant investments on all sites
 - HAPI expansion in Wetteren: + 17 m³



HAPI PRODUCTION LOCATIONS



	Louvain-la-Neuve	Wetteren	Balen
Headquarter	✓		
Sales & Marketing	✓		
R&D	✓	✓	
Pilot Plant	✓	✓	
Production	✓	✓	✓
QC/QA/RA	✓	✓	✓
Purchasing		✓	
Workforce	165	406	127



Overview HAPI capacity

Unit	Site	Level $\mu\text{g}/\text{m}^3 \cdot 8\text{h}$	# reactors	Total reactor volume (L)	Isolation Equipment (L / m ²)
B2	LLN	> 0,1	4	5000	Filter Dryer 800 / 0.8
C2/D2	LLN	> 0,1	12	6550 with Cryogenic 1000 & 250 Hydrogenation 400	Filter Dryer 400 / 0.5 Centrifuge 60 Pressure Filters Plate Dryers
SY1	WTN	> 0,1	6	17200 Preparative Chrom	Filter Dryer 2000 / 2
SY7 unit C	WTN	> 1	4	21000	Filter Dryer 2000 / 2
SY11 unit 2	BLN	> 1	4	30300	Filter Dryer 4000 / 3



Overview HAPI capability

- Multitude of technologies & experience
 - Low temperature (-100°C)
 - Hydrogenation
 - Handling of toxic reagents (cyanide, hydrazine, MeBr, Br₂...)
 - Preparative Chromatography (450mm & 150mm)
 - Freeze Drying
- Bulk botanical counter-current extraction facility
 - Input typically 20MT/day
- Licenced to manufacture Controlled Substances
- Various packaging options



- OEB-banding OmniChem
- Measurement setup
- Interpretation of results
- Practical example
 - Results before
 - Optimisations
 - Results after



OEB – BANDING OMNICHEM

OEB	$\mu\text{g}/\text{m}^3/\text{day}$	Examples
1	>1000	Irritant and not harmful
2	>100-1000	Harmful; mild sensitizers; Therapeutic dose > 50-100 mg/day
3	>10-100	Substances of unknown toxicity not allocated to another OEB Moderate, strong or extreme skin sensitizers Acute toxic (T); harmful to reproduction Therapeutic dose >1-50 mg/day
4	>1-10	Respiratory sensitisers Substances to suspect carcinogenicity; concern over mutagenicity Very (acute) tox; toxic to reproduction or lactation Therapeutic dose \leq 1 mg/day
5	\geq 0,1-1	Very strong experimental evidence for carcinogenicity Substances known to be genotoxic in vivo Therapeutic dose \leq 0,1mg/day



MEASUREMENT SET-UP

- Collection on IOM sampler with glass fiber filter (fixed + personal monitoring)
- Flow rate of pumps : 2 L/min
- Analysis in OmniChem QC lab or external lab
- Surrogate testing & monitoring



MEASUREMENT SET-UP



FIXED MEASURING POINTS



MEASUREMENT SET-UP



PERSONAL
MONITORING



INTERPRETATION OF RESULTS

- OEL defined by own toxicologist
- Time weighted average (8h) is compared to OEL
- If no OEL is defined, the lower limit of the OEB is used as reference.
- The protection factor of RPE (respiratory protection equipment) is not taken into account during evaluation.

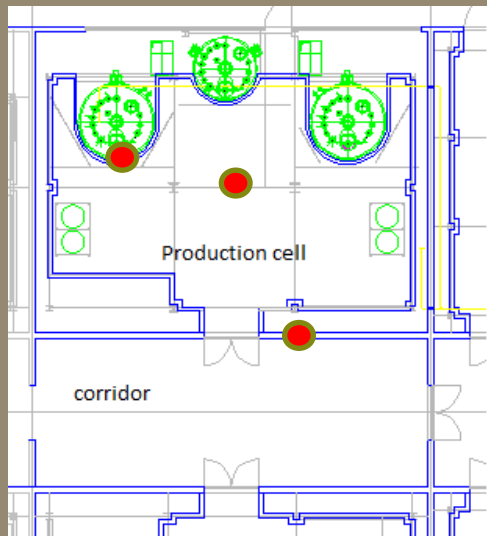


EXAMPLE : DOSING OF OEB-3 PRODUCT VIA REACTOR MANHOLE

- Previous standard way of working
 - Counterweighted valve
 - Local extraction ventilation
- Monitoring campaigns: exposure too high
 - Reality = time pressure
 - Operator dependent
 - → not robust
 - Spread of dust in production cell possible
 - Due to compartmentalisation no product measured in corridors



RESULTS BEFORE



Date	Measured ($\mu\text{g}/\text{m}^3$)	TWA (8h) ($\mu\text{g}/\text{m}^3$)	TWA(8h) / OEL	Type of sample
10/03/2011	8368	244,1	24,41	Personal monitoring
10/03/2011	1524	44,45	4,44	Personal monitoring
10/03/2011	326	9,51	0,95	Stationary: control console
10/03/2011	<16	<0,47	-	Stationary: corridor

Date	Measured ($\mu\text{g}/\text{m}^3$)	TWA (8h) ($\mu\text{g}/\text{m}^3$)	TWA(8h) / OEL	Type of sample
17/09/2012	640	58,67	5,8	Personal monitoring
17/09/2012	1412	129,4	12,9	Personal monitoring
17/09/2012	2830	259,4	25,9	Stationary: just above manhole
17/09/2012	397	36,39	3,6	Stationary: control console
17/09/2012	<16	<1,47	-	Stationary: corridor

Monitored product

1) No OEL defined

2) OEB 3

→ Lower level = $10 \mu\text{g}/\text{m}^3$



OPTIMALISATION

- VIDEO



RESULTS AFTER

Monitored product
OEL 30 µg/m³

Date	Measured (µg/m ³)	TWA (8h) (µg/m ³)	TWA(8h) / OEL	Type of sample
23/08/2012	288	10,20	0,34	Personal monitoring
23/08/2012	368	13,03	0,43	Personal monitoring
23/08/2012	<61	<2,16	0,08	Stationary: just above manhole
23/08/2012	<21	<0,74	0,03	Stationary: control console
23/08/2012	<21	0,74	0,03	Stationary: corridor

Monitored product
OEL 20 µg/m³

Date	Measured (µg/m ³)	TWA (8h) (µg/m ³)	TWA(8h) / OEL	Type of sample
13/02/2012	80	6,00	0,3	Personal monitoring
19/03/2012	nd<5	<0,38	<0,02	Personal monitoring
13/02/2012	nd<5	<0,38	<0,02	Personal monitoring
19/03/2012	<15	<0,38	<0,02	Personal monitoring
13/02/2012	4683	351,23	17,56	Stationary: just above manhole
19/03/2012	52	2,93	0,15	Stationary: just above manhole
13/02/2012	nd<5	<0,38	<0,02	Stationary: control console
19/03/2012	nd<5	<0,38	<0,02	Stationary: control console
13/02/2012	nd<5	<0,38	<0,02	Stationary: corridor
19/03/2012	nd<5	<0,38	<0,02	Stationary: corridor



CONCLUSIONS

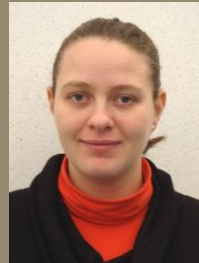
- Robust technique
- Accepted by operators
- Easy to train
- Pragmatic; results without major investments
- Inert conditions in reactor guaranteed

+ GOOD RESULTS AFTER MONITORING!



- Safety team AOC-Wetteren

- Lies Hubau
- Tom Van de Voorde
- Lieven Dieussaert
- Joris De Keijser



- Production engineers SY7 & SY3/4

- Wouter Herwege
- Pierre Claessens

