Evaluation of toxicity and human health risk assessment for 2-Pentanone Oxime

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SUMMARY

BACKGROUND: 2-Pentanone Oxime (2-PO) belongs to oxime class of compounds and has many uses in industrial and commercial applications. It has been proven to be an effective anti-skinning agent in paints, as an isocyanate blocking agent in polyurethane coatings and used as a raw material for the manufacturing of sealant additives. Due to potential workplace exposure, it was important to evaluate the safety of this product to end-users.

RESULTS: Several acute, sub-acute, sub-chronic toxicity studies were conducted to assess the safety of 2-PO. Other than eye irritation, no major acute toxicity concern was observed for this chemical. 2-PO is not a skin sensitizer and is non-genotoxic in rodent bioassay. A 90-day repeated-dose inhalation toxicity study in rats up to the highest achievable vapor concentration of 300 ppm, was conducted to determine the target organ toxicity and no-observed-adverse-effect-concentration (NOAEC). The endpoint from this experiment will be used in deriving the derived no-effect level (DNEL) and evaluate risk to workers. A gene expression analysis was also conducted to determine the hepatotoxicity and carcinogenic potential in rats.

CONCLUSION: Based on the results from several toxicological studies, it is concluded that 2-PO has acceptable human health hazard and risk profile for its intended applications.

STUDY OBJECTIVES

- ❑ Evaluate acute, subacute, sub-chronic toxicity of 2-PO
- ❑ Evaluate genotoxicity property
- ❑ Predict non-genotoxic carcinogenicity potential
- ❑ Evaluate the exposure to workers from paint application
- ❑ Estimate the Risk Characterization Ratio (RCR) and overall safety to painters from the application of 2-PO

MATERIALS AND METHOD

Toxicity Assays	Guideline	Species	Concentrations
Oral Acute	OECD 425	Rat	175, 550, 2000 mg/kg
Inhalation Acute	OECD 403	Rat	300 ppm
Eye Irritation	OECD 405	Rabbit	0.1 ml
Skin Irritation	OECD 406	Guinea pigs	0.4 ml
Skin Sensitization	OECD 406, 429	Guinea pigs	0.4 ml
In vitro (Ames)	OECD 471	Bacteria (5)	Up to 5000 µg/plate
In vitro (Micronucleus +/- S9)	OECD 487	lymphocytes	1012 µg/mL
In vitro (Chrom Ab+/- S9)	OECD 473	lymphocytes	1012 µg/mL
In vivo (CAT, Comet Assay)	OECD 475	Rats	50, 150 and 300 ppm
Repeated Inhalation (14day/90-day)	OECD 413	Rats	50, 150 and 300 ppm
Sub-acute, Repro and Developmental	OECD 422	Rats	15, 50 or 150 mg/kg
Toxicogenomics	NA	Rats	50, 150 and 300 ppm

RESULTS

Acute, Subacute and Sub-chronic Toxicity of 2-PO

Available assays	Toxicity End Points	CLP Classification and Remark
Oral Acute	LD50=1133 mg/kg	Category 4; Not a major route of exposure
Inhalation Acute	LC50 > 300 ppm (No mortality)	Not classified; Major Route of exposure for paint application
Eye Irritation	Moderately-Severely Irritating	Category 2
Skin Irritation	Not an irritant	Not classified
Skin Sensitization	Not a sensitizer	Not classified
STOT (Oral or Inhalation)	No narcotic effect observed	Not classified
Sub-chronic	NOAEC = 300 ppm	No adverse effect up to 300 ppm

Genotoxicity of 2-PO

Available assays	Results	Overall Conclusion
In vitro (Ames +/- S9)	Not genotoxic	Not Classified as mutagenic. In animal experiments 2-PO was not genotoxic. Therefore, not expected to be genotoxic in humans. No chromosomal aberration was observed in *in vivo* assay.
In vitro (Micronucleus +/- S9)	Not genotoxic	
In vitro (Chrom Ab+/- S9)	Positive only with S9	
In vivo (Comet Assay)	Not genotoxic	
In vivo (Chrom Ab)	Not genotoxic	

Toxicogenomic Analysis for Carcinogenicity in Liver

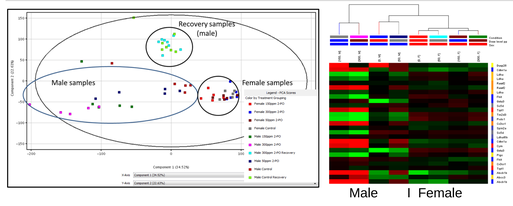

Figure 1: Principal Component Analysis (A) and hierarchical clustering of genes (B). PCA analysis for exposure and recovery groups implied reversal of effects in male in 300 ppm-group.

Toxicogenomic Findings

- At 150 and 300 ppm of 2-PO in male rats caused increased expression of genes involved in xenobiotic metabolism, namely GSTa3, GSTm and UGT
- Analysis of toxicological pathways by IPA™ demonstrated possible involvement of CAR and PXR, however the absence of an increase of CYP2B and liver hypertrophy or hyperplasia makes this finding biologically not significant
- Lack of CYP4A induction suggests a lack of conventional activation of PPAR-α
- No strong evidence for AhR activation in the absence of CYP1A1 induction
- No mitogenic response was observed either in male or in female liver
- Gene expression shifts back to baseline following recovery suggests that the effects are transient and dependent of exposure magnitude of dose

Toxicogenomic Conclusion

- Based on pathway analysis, magnitude of gene expression, reversibility of effects and in corroboration with biological findings, it can be stated that 2-PO is likely to have no Non-Genotox Carcinogenic potential

Exposure Analysis and Risk Assessment

Different Paint Samples	Measured Exposure Value (mg/m3)			
	2-PO at 0.5%		2-PO at 0.9%	
	On Painter	100 cm away	On Painter	100 cm away
1	0.90	0.46	1.78	0.67
2	2.47	1.38	3.83	1.79
3	0.91	0.35	1.57	0.83
4	1.65	0.75	3.22	1.55
5	1.38	1.50	2.57	2.54

- **Derived-No-Effect-Level (DNEL):** Using REACH guidance Chapter R.8The DNEL for workers (long-term Systemic) was established at 25 mg/m^3
- **Risk Characterization Ratio (RCR)** = Exposure/DNEL; Risk is acceptable if RCR is <1

Different Paint Samples	Risk Characterization Ratio			
	2-PO at 0.5%		2-PO at 0.9%	
	On Painter	100 cm away	On Painter	100 cm away
1	0.04	0.02	0.07	0.03
2	0.08	0.06	0.15	0.07
3	0.12	0.01	0.06	0.03
4	0.16	0.03	0.13	0.06
5	0.20	0.06	0.10	0.10

- Acceptable for all paint application scenarios

CONCLUSIONS

❑Except eye irritation and oral toxicity, there are no acute and chronic health hazard concerns for 2-PO in paint applications

❑Repeated-dose inhalation study demonstrated no significant adverse effects in rats at 300 ppm (NOAEC), the highest tested concentration

❑Overall, 2-PO is not a genotoxic compound. It was not genotoxic in several *in vivo* animal models

❑Toxicogenomic analysis did not find any potential Non-Genotoxic Carcinogenic pathways in liver

❑Read-across to other Oximes is not appropriate due to available data for risk assessment

❑ Exposure assessment followed by risk assessment demonstrated acceptable risk for its intended uses

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