Research Article

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Permitted Daily Exposure for 2-Chloropropane as a Residual Solvent in Pharmaceuticals.

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ABSTRACT

The manufacture and use of drugs and chemicals have brought numerous benefits to modern society. However, unintended exposure to these chemicals in the final drug formulation can cause a significant health hazard to the Patients and unintended exposure to these agents at the manufacturing workplace can cause a significant health hazard to the workers at the manufacturing plant. Residual Solvants in Pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacturing of the drug substance or excipients, or in the preparation of drug products. The aim of the current publication is to determine the Permitted daily Exposure (PDE) and Occupational Exposure Limit (OEL) of 2-Chloropropane, which is a commonly used solvent in Pharmaceutical industry. The following Regulatory Guidelines were followed while deriving the PDE value for 2-chloropropane, ICH Q3C, ICH Q3D, EMA/CHMP/CVMP/SWP/169430/2012. A Literature Review was conducted to identify toxicity studies of 2-Chloropropane. Hazard and sensitive endpoints were determined. Based on the No Observed Adverse Effect Level/Concentration (NOAEL/NOAEC) and Lowest Observed Adverse Effect Level/Concentration (NOAEC) reported from battery of toxicology studies like repeat dose, reproductive and development toxicity studies, the PDE value and OEL value was calculated.

Keywords : Permitted Daily Exposure, Occupational Exposure Limit, 2-Chloropropane, Residual Solvant, Cleaning Validation, Multipurpose/Shared Manufacturing Facility, Cross Contamination.

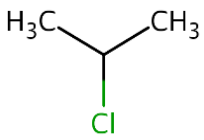
INTRODUCTION

The objective of the present manuscript is to recommend acceptable amounts of 2-Chloropropane residual solvent in pharmaceutical for safety of the Patient and occupation exposure at work place for the safety of the worker. Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacturing of the drug substance or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. There is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. 2-chloropropane is the common industrial solvent which is used for pharmaceutical manufacturing, but it is not listed under ICH Q3C, hence the PDE value and OEL value derived in this review might be useful for the scientists working in Pharmaceutical Industry. According to the Regulatory Guideline one has to be compliant to cleaning validation PDE acceptance criteria.

Although traditional approaches such as the fraction of therapeutic dose are at times used as OEL value, it is less reliable compared to the value derived based on full review of pharmacology and toxicology and the clinical adverse effects of the drug (health-based PDE/OEL). In view of the subjective nature of some of the assumptions involved in the PDE/OEL/HBEL derivation, it is important that organizations develop internal guidance/SOP and that the derivation is well described and documented in a detailed toxicology monograph. Also, to ensure that derived values are scientifically defensible and acceptable to regulatory agencies, documented evidence should be available with regard to the experience and the skill set of the toxicologist, so also the evidence for a review by an expert toxicologist. It is also to be kept in mind that when PDE/OEL/HBELs are derived using limited data set or when new data becomes available, a review of the established value may be considered and if appropriate, the PDE/OEL/HBEL should be revised.[i,ii,iii,iv,v,vi]

Journal of Toxicological Research (ISSN 2996-1823)

I. Identification: [i,ii,iv]

Name	**2-Chloropropane**
Synonyms	Isopropyl chloride Propane,2-chloro Isopropylchloride 2-propyl chloride Isoprid 2-CP
CAS No.	75-29-6
Molecular Formula	C3H7Cl
Structural Formula	
Molecular weight	78.54 g/mol

II. Chemical and Physical Properties : [i,ii,iv]

Physical State:	**Colorless liquid**
Molecular Weight:	78.54
Conversation Factors:	1 ppm = 3.21 mg/m3; 1 mg/m3 = 0.31 ppm
Melting Point:	-117.2 °C (-179 °F) at 760 mm Hg
Boiling Point:	35.7 °C (96.3 °F) at 760 mm Hg
Vapor Pressure:	515.3 mm Hg at 25 °C (77 °F)
Saturated Vapor Conc.:	~ 678,000 ppm at 25 °C (77 °F) (calculated)
Odor Description:	Chloroform-like, mildly sweet Odor
Threshold:	Limited odor. Some subjects could not detect 500 ppm 2-Chloropropane vapor.
Flammability Limits:	2.8 – 10.7% (in air at 25 °C)
Flash Point:	-32 °C (-26 °F) (closed cup)
Autoignition Temp.:	593°C (1100 °F)
Specific Gravity:	0.8617 at 20°C (68 °F)
Vapor Density:	2.7 (air = 1)
Solubility:	In water = 3.05 g/L at 25 °C; soluble in benzene, acetone, and methanol; miscible with alcohol and ether
Stability:	Normally stable Reactivity and Incompatibilities: Can react vigorously with oxidizing materials

Animal toxicity data [i,ii,iii,iv]

Acute Toxicity Studies

Oral

In an acute oral toxicity study (OECD Guideline 401, GLP study), in rats 5/sex/dose, 2-Chloropropane was administered at doses 2000 mg 2-Chloropropane/kg body weight in oleum arachidis (vehicle) by gavage. The animals were observed for 14 days after administration and body weights were taken at days 0, 7, and 14. Animals were observed for clinical signs of toxicity 20

Journal of Toxicological Research (ISSN 2996-1823)

minutes and 1, 2, 3, 6, and 24 hours following administration and once daily until day 14. Animals were necropsied after the observation period. No mortality was reported over the 14-day observation period, and no clinical signs of toxicity were reported. Body weight gains were normal in all animals and no 2-Chloropropane related findings were reported at necropsy. Therefore, the oral LD50 for 2-Chloropropane in male and female rats was determined to be greater than 2000 mg/kg body weight.

Dermal

In an acute dermal toxicity study (OECD Guideline 402, GLP study), in Wistar rats 5/sex/dose, 2-Chloropropane in oleum arachidis (vehicle) was applied for 24 hours at 2000 mg/kg body weight. The 2-Chloropropane was applied to the shaved backs of the animals and covered with a porous gauze dressing and Elastoplast. After 24 hours, the dressing was removed, and the animals were observed for clinical signs of toxicity 20 minutes and 1, 2, 3, 6, and 24 hours afterwards, and once daily thereafter. Dermal irritation was evaluated daily according to a scheme based on the Draize method. Body weights were recorded on day 0, 7, and 14. Animals found dead and animals surviving till the end of the 14-day observation period were necropsied and gross pathological examinations were performed. No mortality was reported, and no abnormal clinical signs of toxicity were reported. In addition, all animals showed normal body weight gain and there were no signs of erythema or edema, and no 2-Chloropropane related findings at necropsy were reported. Therefore, the dermal LD50 for 2-Chloropropane in male and female rats was determined to be greater than 2000 mg/kg body weight.

In an another acute dermal toxicity study (OECD Guideline 402, GLP study), in Wistar rats (5/sex/dose), 2-Chloropropane was applied at doses 2000 mg 2-Chloropropane/kg body weight in oleum arachidis (vehicle) for 24 hours with an occlusive dressing. The animals were observed for 14 days and necropsy was performed on all animals after the administration period. There were no mortalities, no adverse clinical signs, and no adverse findings at necropsy. The dermal LD50 in male and female rats was determined to be greater than 2000 mg kg body weight.

Inhalation

In an acute inhalation toxicity study (OECD Guideline 403, GLP study), in rats 5/sex/dose, 2-Chloropropane exposed to 1.94 or 6.54 mg/L for 4 hours via nose only exposure in test chambers. During the exposure, continuous analysis of the atmosphere was performed. The animals were observed for clinical signs of toxicity throughout exposure and daily for 14 days thereafter. Necropsy was performed at the end of the observation period. No mortality was reported during the study period, and gross macroscopic inspection at necropsy did not reveal any 2-Chloropropane related adverse effects. Therefore, the inhalation LC50 for 2-Chloropropane in male and female rats was determined to be greater than 6.54 mg/L. In an another acute inhalation toxicity study (OECD Guideline 403, GLP study), in rats 5/sex/dose, 2-Chloropropane exposed to 133 g per cubic meter 2-Chloropropane vapour for 7 hours via whole-body exposure in test chambers. During the exposure, continuous analysis of the atmosphere was performed. The animals' activity was increased for a short time, but within 10 minutes all animals were deeply narcotized. All animals died within 1 hour and gross necropsy revealed hyperemic lungs in all animals.

Table 1: Acute Toxicity Studies (LD50 and LC50 value)[i,ii,iii,iv]

	Mice	Rat	Guinea Pig
Oral	LD50: >3200 mg/kg	LD50: >2000 mg/kg	LD50: >3000 mg/kg
	LD50:1300 mg/kg	LD50: >3200 mg/kg	
		LD50: 5000 mg/kg	
Dermal	-	LD50: 1100 mg/kg	-
		LD50: >2000 mg/kg	
Inhalation	LC50: 119000 mg/m3	LC50: 120000 mg/m3	-
		LC50: >6.54 mg/L	
		LC0: 2030 ppm (5 males and 5 females; Nose-only exposure); 4 hours	
		LC0: 8000 (3 animals); 4 hours	
		LC100: Saturated vapor exposure @ 23°C (3 animals)	

Eye Irritation

Rabbits: A volume of 0.1 mL of 2-CP was instilled into the left conjunctival sac of six animals. 2-Chloropropane produced low-grade conjunctival effects (redness and swelling) at the 1 and 24 hour observation intervals. No findings on the cornea or iris were observed. All irritation resolved by 48 hours. 2-CP was classified as a non-irritant for the eye based on European Economic Commission (EEC) guidelines.

Skin Irritation

Rabbits: A volume of 0.5 mL of 2-Chloropropane was applied on the intact and abraded dermal surface of the back of six animals. Test sites were wrapped for 4 hours and then

Journal of Toxicological Research (ISSN 2996-1823)

unwrapped, gently cleaned (if necessary) and evaluated. No erythema or edema was observed. 2-CP was classified as non-irritating on skin based on EEC guidelines.

Skin Sensitization

Guinea Pigs: 2-Chloropropane was tested for the potential to cause skin sensitization according to the experimental design of Magnusson and Kligman. Twenty test and 20 control animals were studied. No irritation or sensitization was observed following challenge exposures.

Repeat Dose toxicity Studies[i,ii,iii,iv]

In a series of investigations studies in 1950, the inhalation toxicity studies of 2-Chloropropane were conducted. Both acute and subchronic tests were reported. Mice (10 females), rats (20 males and 20 females), guinea pigs (8 males and 8 females), rabbits (2 males and 2 females) and monkeys (2 females) were exposed by whole body inhalation to 1000 ppm 2-Chloropropane for approximately six months (7 hours/day, 5 days/week, 127 exposures). Air exposed controls and unexposed controls were run for valid comparison. No significant treatment-related changes were observed in mortality, appearance, growth, behavior, or final average body and organ weights. Microscopic examination of the tissues revealed adverse changes in the lungs of female rabbits and monkeys (edema or pneumonitis) and in the livers of all exposed species. In general the liver pathology was characterized by necrosis of the parenchymal cells of the portal region. Repeated exposure to 1000 ppm 2-Chloropropane also caused kidney injury in guinea pigs, rabbits and monkeys characterized by tubular degeneration of the epithelium with some necrosis.

In a similar, but separate experiment, rats (24 males and 24 females), guinea pigs (12 males and 12 females), rabbits (2 males and 2 females) and dogs (2 females) were repeatedly exposed to 500 ppm of 2- Chloropropane vapor for six months. At 500 ppm no treatment-related adverse effects were observed in any of the exposed animals.

Rat study

In a 4-week repeat dose inhalation toxicity study in Alderley Park SPF rats/sex, 2-Chloropropane was exposed at concentrations of 250 or 1000 ppm for 6 hours/day, five days/week for 4 weeks (20 exposures). Rats from both groups completed this exposure regimen without mortality or other clinical signs of toxicity. Rats exposed to 1000 ppm showed liver injury characterized by extensive vacuolation and necrosis. No adverse effects were seen in rodents exposed to 250 ppm.

In a 90-day repeat dose inhalation toxicity study (OECD Guideline 413, GLP study), in Sprague Dawley rats 10/sex/dose were exposed to 2-Chloropropane vapor at target concentrations of 0 (Sham Control), 250, 500, or 1000 ppm (analytical concentrations of 255, 492, and 996 ppm, respectively) for six hours per day, seven days per week. A second high-concentration exposure group (satellite) was simultaneously exposed for 90 days and then held for an additional 30 days to determine the reversibility of any adverse findings identified in the main study groups. There were no 2-Chloropropane related mortality or changes in the general condition and behavior of the rats and no signs of neurotoxicity were observed. There were no 2-Chloropropane related findings for ophthalmology, hematology, clinical chemistry, and urine parameters, gross pathology examinations, organ weights, histopathological examinations (including liver and kidneys), and determination of laryngeal epithelial thickness. A slight decrease in food consumption and in body weight gain was observed only for the male rats in the highest (1000 ppm) concentration group. An effect of the 2-Chloropropane with regard to these findings could not be excluded. Based on the data, a NOEC of 500 ppm was derived based on the lack of clear-cut toxic effects of 2-Chloropropane exposure at this concentration. The study Director indicated that the 1000 ppm concentration was considered to be at the border of the lowest observed effect concentration determined in the study. Following a review of the data, it was concluded that the decreased food consumption and body weights observed in the 1000 ppm male rats were not adverse. This was based on the small magnitude of the observed changes, the absence of any other 2-Chloropropane related findings, and because a pre-existing 5% lower body weight was noted in 1000 ppm male rats prior to the start of the study. Therefore, the NOAEL for this study was considered to be 1000 ppm (analytical concentration of 996 ppm, corresponding to 3252 mg/m3 at 1 atm and 20 ° C). Histopathological evaluation included reproductive and endocrine organs, neurological tissues and immune system tissues. No treatment-related mortality or changes in general appearance or behaviour was reported in any treatment group. A slight decrease in food consumption and body weight was reported in male rats exposed to 1000 ppm. All other measured parameters including blood and clinical chemistry, organ weight determinations, histopathological evaluations (including liver and kidneys) and determination of laryngeal epithelial thickness showed no significant treatment-related adverse effects. Based on these results, 500 ppm was reported as a clear NOEL. No supportive studies were located.

Journal of Toxicological Research (ISSN 2996-1823)

Table 2 : Summary of the Results and effects observed in repeat dose inhalation toxicity studies considered for Health Hazard Assessment.[i,ii,iii,iv]

Species	Duration	Dosage	NOAEL/LOAEL
Mice	6-month	0 or 1000 ppm 7 hours/day 5 days/week	-
Rat	4-week	250 or 1000 ppm 6 hours/day 5 days/week	NOAEL: 250 ppm
Rat	3-month	0, 250, 500, 1000 ppm 6 hours/day 7 days/week	NOE(C/L): 500 ppm NOAEC: 1000 ppm NOAEC: 3252 mg/m3
Rat	6-month	0 or 1000 ppm	-
Rat	6-month	500 7 hours/day 5 days/week	NOAEL: 500 ppm
Guinea pig	6-month	0 or 1000 ppm 7 hours/day 5 days/week	-
Guinea pig	6-month	500 ppm 7 hours/day 5 days/week	NOAEL: 500 ppm
Rabbit	6-month	0 or 1000 ppm 7 hours/day 5 days/week	-
Rabbit	6-month	500 ppm 7 hours/day 5 days/week	NOAEL: 500 ppm
Monkey	6-month	0 or 1000 ppm 7 hours/day 5 days/week	-
Dog	6-month	500 ppm 7 hours/day 5 days/week	NOAEL: 500 ppm

Reproductive/ Developmental Toxicity studies [i,ii,iii,iv]

In an Embryo-Fetal Development study, Pregnant Sprague–Dawley rats were exposed to 2-Chloropropane by inhalation at concentrations of 250, 500, 1000 or 2700 ppm from day 6 to 15 of gestation. No clinical signs of toxicity were observed in any of the treated dams. Dark red and beige foci were found in the lungs of treated dams at 2700 ppm (12/20) and to a lesser extent at 1000 ppm (2/20). No treatment-associated increase in fetal malformations was observed at any exposure level. At the highest concentration a slight increase in skeletal variations was found (86.3% compared to 72.0% in the controls). The results show that 1000 ppm was at or near the threshold for maternal toxicity (NOEL/LOEL). The NOEL for fetal effects was 1000 ppm.

Journal of Toxicological Research (ISSN 2996-1823)

Table 3 : Summary of the Results and effects observed in Reproductive and Developmental Inhalation toxicity studies considered for Health Hazard Assessment.[i,ii,iii,iv]

Species	Duration	Dosage	NOAEL/LOAEL
Rat	Embryofetal development study GD 6 to 15	250, 500, 1000, 2700 ppm 0.61, 1.43, 2.66, 6.67 mg/L 6 hours/day	NOEL: 1000 ppm (Fetal toxicity) NOEL: 500 ppm ~1.43 mg/L (Maternal toxicity) NOAEC: 1.43 mg/L (1430 mg/m3) NOAEC: 6.67 mg/L (6670 mg/m3)
Rat	GD 6 to 15	0.81, 1.62, 3.23/8.72 mg/L 6 hours/day	-

Genotoxicity/Mutagenicity[i,ii,iii,iv]

In vitro

2-Chloropropane was mutagenic to S. typhimurium after metabolic activation when tested in desiccators. No mutagenic response was observed in a standard S. typhimurium/ microsome test with 4 strains of bacteria and doses up to 10,000 µg/plate. 2-Chloopropane failed to show any evidence of genotoxicity in a battery of short-term tests including HGPRT gene mutation in V79 cells, DNA single-strand breaks in V79 cells, unscheduled DNA synthesis in human fibroblasts and chromosomal aberrations in human blood lymphocytes.

In vivo

2-Chloropropane was not genotoxic in a mouse micronucleus test. Male and female mice were administered 2-Chloropropane at 2000 mg/kg by intraperitoneal injection and bone marrow was harvested for study at 24, 48 and 72 hours post-dosing. 2-Chloopropane exposure failed to produce an increase in the frequency of micronuclei in polychromatic erythrocyte stem cells.

Metabolism/Pharmacokinetics[i,ii,iii,iv]

It has been reported that 2-Chloropropane is enzymatically dechlorinated in vitro by rat liver microsomes. Additional studies suggest that cytochrome P450 may catalyze this reaction.

Human Use and Experience

Only a limited amount of industrial hygiene data is available for 2-Chloropropane. Individual worker TWA exposures were all below 0.11 ppm in a plant that used 2-Chloropropane as a chemical intermediate. The workers who were monitored in this study performed a variety of jobs at the plant including, process operators, pipe fitters, electricians, welders, machinists, and foremen. Exposures to 2-Chloropropane were slightly higher for maintenance personnel when cleaning lines and working on pumps (0.1–0.17 ppm). Recent exposure studies of 2-Chloropropane in foam fabrication field trials indicate TWA workplace atmospheres of less than 6 ppm.

Summary

Acute toxicity data indicates a low order of toxicity by oral, dermal and inhalation routes of exposure. Based on EEC guidelines, 2-Chloropropane was tested and found not to be an eye or skin irritant. 2-Chloropropane did not induce skin sensitization in guinea pigs. 2-Chloropropane is not genotoxic based on a robust battery of mammalian cell and whole animal genotoxicity tests. However, in one instance, when 2-Chloropropane was tested in a desiccator with S. typhimurium, 2-Chloropropane was mutagenic following metabolic activation.

A wide variety of animal species, mice, rats, guinea pigs, rabbits and monkeys, were exposed to 1000 ppm 2-Chloropropane vapor for six months in the 1950s. This exposure regimen revealed the critical effect to be adverse effects in the liver found in all species. A NOEL could not be established because 1000 ppm was the only exposure level used in the experiment. In follow up experiments using rats, guinea pigs, rabbits and dogs, a 500 ppm exposure regimen resulted in no treatment-related adverse effects. More recently (1993), a study using rats and a range of exposures (0, 250, 500, 1000 ppm) indicated minimal adverse effects [decreased body weight and food consumption; no liver or kidney pathological changes] in the 1000 ppm exposure group. This study included an extensive histopathological evaluation, clinical chemistry and a recovery group. Based on the results of these experiments, 500 ppm was a clear NOEL.

Developmental effects of 2-Chloropropane vapor have also been evaluated in rats. Pregnant rats showed limited evidence (color changes in the lung) of maternal toxicity at 1000 ppm (LOAEL). No fetal malformations were produced. An increase in skeletal variations in the exposed fetus was observed at 2700 ppm. The NOEL for fetal toxicity was 1000 ppm. The NOEL for maternal toxicity was 500 ppm.

Journal of Toxicological Research (ISSN 2996-1823)

Regulatory Status[i,ii,iii,iv]

ECHA DNELs:

Worker – Inhalation = 91.5 mg/m3

Worker – Dermal = 132 mg/kg bw

General Population – Oral = 4.7 mg/kg bw

General Population – Inhalation = 16.3 mg/m3

General Population – Dermal = 47.2 mg/kg bw

A WEEL guide of 50 ppm as an 8-hr TWA should allow an adequate margin of safety to protect against liver injury and potential adverse effects to the fetus.

RECOMMENDED WEEL[iv]

8-hr time-weighted average (TWA): 50 ppm (161 mg/m3).

Study considered for PDE and OEL determination.[i,ii,iii,iv]

Based on above studies the lowest NOE(L/C) was reported in 9-month repeat dose inhalation toxicity study in rats and was considered for PDE determination.

In 3-month repeat dose inhalation toxicity study in rats, 2-chloropropane was exposed at doses 0, 250, 500, 1000 ppm, 6 hours/day, 7 days/week. The study details have already been discussed above. NOEL 500 ppm was reported.

Dose conversions:[vi]

$$500\ ppm = \frac{500 \times 78.54}{24.45} = 1606.13\ mg/m3 = 1.606\ mg/l$$

$$\text{For Continuous Dosing: } \frac{1.606 \times 6}{24} = 0.401\ mg/l$$

$$\text{Daily Dose: } \frac{0.401\ mg/l \times 290\ l/day}{0.425\ kg} = 273.62\ mg/kg/day$$

Rat respiratory volume: 290 L/day

Rat body weight: 0.425 kg

Table 4

Application of Adjustment Factorsv,vi,vii ,viii		
FACTOR	**VALUE APPLIED**	**RATIONAL**
F1: A factor to account for extrapolation between species.	5	Extrapolation from rat to humans
F2: A factor to account for variability between individuals	10	Variability between individuals
F3: A variable factor to account for toxicity studies of short-term exposure	5	3-month study in rodents
F4: A factor that may be applied in cases of severe toxicity. e.g., nongenotoxic, carcinogenicity, neurotoxicity or teratogenicity.	1	No severe adverse effects reported
F5: A variable factor that may be applied if the no-effect level was not established	1	Because NO(A)EL/NOEC value was determined.

PDE value Calculation

$$PDE = \frac{NO(A)EL/NOEC\ X\ Weight\ adjustment}{F1X\ F2X\ F3\ X\ F4X\ F5} = \frac{273.62\ X\ 50}{5\times10\times5\times1\times1} = 54.72\ mg/day$$

Journal of Toxicological Research (ISSN 2996-1823)

OEL Calculation

Occupational exposure limits (OELs) are maximum acceptable air concentrations that are used as reference parameters for the protection of workers from overexposure to chemical substances by inhalation. Occupational exposure limit calculation can be done using the formulae: [ix,x,xi]

$$OEL = \frac{NO(A)EL/NOEC \text{ X Weight adjustment}}{F1X\ F2X\ F3\ X\ F4X\ F5X\ \alpha\ X\ V}$$

Table 5

V	Breathing rate in workers typically is assumed to be 10 m3/8-hour workday
α	Toxicokinetic adjustment
Bioavailability Adjustment Factor (BAF or BCF or α)	In cases, when data from the relevant route are not available, bioavailability adjustments are useful to ensure adequate exposure protection. If the differences are quantitatively relevant, a bioavailability correction factor (BCF) or (BAF) should be applied, resulting in route-specific ADE/PDE/OEL values. A BCF, also referred to as alpha (α) in some references, is defined as the bioavailability via the exposure route of interest divided by the bioavailability via the route used in the critical study.
α	$\frac{\%\text{systemic bioavailability for the route of interest}}{\%\text{systemic bioavailability for the dose route used as the basis for the PoD}}$
α	α = 1, since same inhalation route of administration study was considered for the assessment and no further Toxicokinetic correction is required.

Note: PoD – Point of departure

$$OEL = \frac{NOAEL \text{ X BODY WEIGHT}}{F1X\ F2X\ F3\ X\ F4X\ F5X\ \alpha\ X\ V} = \frac{273.62 \times 50}{5{\times}10{\times}5{\times}1{\times}1{\times}1{\times}10} = 5.472 \text{ mg/m3}$$

OEB Determination [xiii,xiv]

Table 6

Occupational Exposure Limit (OEL)	Occupational Exposure Band (OEB)
> 1 mg/m3	A
> 0.1 and < 1 mg/m3	B
> 0.01 and < 0.1 mg/m3	C
> 0.001 and < 0.01 mg/m3	D
≤ 0.001 mg/m3	E

2-Chloropropane = A

CONCLUSION

In order to protect patient health and worker health, PDE and OEL is widely being used as a risk assessment tool against which safety measures to patients and exposure control measures are implemented at the workplace. One of the most common approach employed in the derivation of PDE and OEL is the safety factor approach according to ICH and EMEA Guidelines, which identifies a dose (NOAEL/LOAEL) devoid of any severe adverse effects from non-clinical and clinical experience and refined further by use of various safety factors to account of uncertainties involved in the extrapolation. This approach is based on the assumption that there exists a dose up to which no adverse effect are expected (threshold dose); however, this may not be true for a small set of compounds, especially genotoxic carcinogens, where any level of exposure is considered to be associated with a risk of cancer. PDE and OEL derivation in such situation is based on the principle of acceptable risk

level. Regardless of the method employed, considerable amount of toxicologist professional judgement is required to develop a PDE and an OEL which is not overly conservative while ensuring that the derived value is protective enough from the critical adverse effects of the compound. Compared to industrial chemicals, pharmaceuticals/APIs have an advantage in that pharmacology and toxicology of the drug is well characterized, therefore making the derivation of PDE and OEL more reliable.

In conclusion, conservatively, PDE value for 2-Chloropropane was determined to be 54.72 mg/day and OEL value for 2-Chloropropane was determined to be 5.472 mg/m3.

OEB category for 2-Chloropropane was determined to be OEB: A.

The derived PDE value is expected to be protective of the systemic toxicity effects observed under clinical settings. The calculated PDE value represents a sufficient margin of safety for patients.

The derived OEL value is expected to be protective of the systemic toxicity effects observed under occupational settings. The calculated OEL value represents a sufficient margin of safety for workers

REFERENCES

1. ECHA, REACH Dossier, Chemical Name: 2-Chlorpropane, CAS No. 75-29-6, **https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15853/7/1** accessed on 03rd Apr 2023.

2. US EPA, Provisional Peer Reviewed Toxicity Values for 2-Chloropropane (CASRN 75-29-6), EPA/690/R-05/012F Final 8-22-2005, **https://cfpub.epa.gov/ncea/pprtv/documents/Chloropropane2.pdf** accessed on 03rd Apr 2023.

3. GHS Classification, Chemical Name: 2-Chlorpropane, CAS No. 75-29-6, **https://www.nite.go.jp/chem/english/ghs/08-mhlw-0071e.html** accessed on 03rd Apr 2023.

4. OARS WEEL, Chemical Name: 2-Chlorpropane, CAS No. 75-29-6, **https://tera.org/OARS/WEELS/2-Chloropropane%20WEEL%20public%20comment.pdf** accessed on 03rd Apr 2023.

5. Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities: EMA/CHMP/ CVMP/ SWP/169430/2012, 20 November 2014. Available at: **http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf**, accessed on 03rd Apr 2023.

6. INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE ICH HARMONISED GUIDELINE IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C(R8) Current Step 4 version dated 22 April 2021 **https://database.ich.org/sites/default/files/ICH_Q3C-R8_Guideline_Step4_2021_0422_1.pdf**, accessed on 03rd Apr 2023.

7. EMA, ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, 25 August 2015, EMA/CHMP/ICH/83812/2013, Committee for Human Medicinal Products, **https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m7r1-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit_en.pdf**, accessed on 03rd Apr 2023.

8. EMA, ICH guideline M7 (R2) Addendum: Application of the Principles of the ICH M7 Guideline to Calculation of Compound-Specific Acceptable Intakes; Draft version 06 Oct 2021, **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m7r2-addendum-application-principles-ich-m7-guideline-calculation-compound-specific-acceptable** accessed on 03rd Apr 2023.

9. EMA, ICH guideline Q3D (R1) on elemental impurities, 28 March 2019, EMA/CHMP/ICH/353369/2013, Committee for Human Medicinal Products, **https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-32.pdf**,

10. EMA, ICH guideline Q3D (R2) on elemental impurities, 28 September 2020, EMA/CHMP/ICH/353369/2013, Committee for Medicinal Products for Human Use, **https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-q3d-r2-elemental-impurities-step-2b_en.pdf**, accessed on 03rd Apr 2023.

11. Ku RH. An overview of setting occupational exposure limits (OELs) for pharmaceuticals: Setting appropriate occupational exposure limits is an integral component in assuring the health and safety of workers. Chemical Health & Safety. 2000 Jan 1;7(1):34-7. **https://pubs.acs.org/doi/full/10.1021/acs.chas.8b07110**, accessed on 03rd Apr 2023.

12. Establishment of Occupational Exposure Limits (OELs) to protect Workers in Chemical/Drug Manufacturing Plants K.S. Rao M.V.Sc. Ph.D., DABT and Sebastian Joseph M.V.Sc., ERT., DABT **https://gallery.mailchimp.com/cc4570b06ad310bc5da5c7d2e/files/8fedbf20-ad3b-4266-986a-aca970f460b0/12.Establishment_of_OELs.pdf**, accessed on 03rd Apr 2023.

13. Dankovic DA, Naumann BD, Maier A, Dourson ML, Levy LS. The scientific basis of uncertainty factors used in setting occupational exposure limits. Journal of occupational and environmental hygiene. 2015 Nov 25;12(sup1):S55-68. **https://pubmed.ncbi.nlm.nih.gov/26097979/** , accessed on 03rd Apr 2023.

14. Reichard JF, Maier MA, Naumann BD, Pecquet AM, Pfister T, Sandhu R, Sargent EV, Streeter AJ, Weideman PA. Toxicokinetic and toxicodynamic considerations when deriving health-based exposure limits for pharmaceuticals. Regulatory Toxicology and Pharmacology. 2016 Aug 15; 79: S67-78. **https://www.sciencedirect.com/science/article/abs/pii/S0273230016301404?via%3Dihub** accessed on 03rd Apr 2023.

15. Globally harmonized system information on health hazard banding available at **http://www.tera.org/OARS/Presentations/Hazard%20Banding%20Workshop%20IHRT.pdf**, accessed on 03rd Apr 2023.

16. The NIOSH Occupational Exposure Banding Process: Guidance for the Evaluation of Chemical Hazards, External Review Draft, March 8, 2017, DEPARTMENT OF HEALTH AND HUMAN SERVICES, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, **https://www.researchgate.net/profile/Varun_Ahuja/post/How_to_define_OEB_category_of_chemical_using_OEL/attachment/5bfe0bd63843b0067547afd0/AS%3A697782956486658%401543375829941/download/NIOSH+2017+Occupational+Exposure+Banding+process_guidance+for+the+evaluation+of+chemical+hazards.pdf** , accessed on 03rd Apr 2023.