
Clopidol

(CAS No: 2971-90-6)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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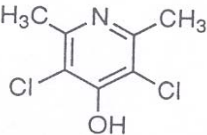
1 Introduction

The present document contains the assessment of the health hazard of clopidol by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The evaluation of the toxicology of clopidol has been based on the review by the American Conference of Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in May 2000, literature was searched in the databases Toxline, Medline, and Chemical Abstracts covering the periods 1981 until May 2000, 1966 until May 2000, and 1937 until April 2000, respectively, and using the following key words: clopidol; methylchloropindol; 4-pyridinol, 3,5-dichloro-2,6-dimethyl-; or 2971-90-6. The final literature search was carried out in Medline and Toxline in January 2003.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	clopidol
synonyms	:	4-pyridinol, 3,5-dichloro-2,6-dimethyl-; methylchloropindol; metichlorpindol; clopindol
molecular formula	:	C ₇ H ₇ Cl ₂ NO
structural formula	:	
CAS number	:	2971-90-6

3 Physical and chemical properties

molecular weight	:	192.04
boiling point	:	not available
melting point	:	>320°C
flash point	:	not available
vapour pressure	:	not available
solubility in water	:	insoluble
log P _{octanol/water}	:	2.71 (estimated)
conversion factors	:	not applicable

Data from ACG99, Bud96, <http://esc.syrres.com>.

Clopidol is a white crystalline powder (ACG99).

4 Uses

Clopidol is used as a coccidiostatic agent in poultry (ACG99).

5 Biotransformation and kinetics

After single or multiple oral doses of 16 mg/kg bw of ¹⁴C-clopidol to rabbits, the compound was rapidly absorbed and excreted via the urine for 90% or more within 24 hours after (final) dosing. Following repeated daily oral doses, no accumulation of radioactivity occurred in the tissues and no radioactivity was detected in the expired air. In the urine, 47% of the radioactivity was from unchanged clopidol, 32% from a hydroxylated product, and 20% probably from the *O*-glucuronide of the hydroxylated product. Thirty-two hours after the last of 5 daily doses, no radioactivity was detected in the tissues or plasma of the rabbits. No half-life time was calculated (Cam75).

After a single oral dose of 50 mg ³⁶Cl-clopidol to rats, about 10% of the radioactivity was still in the stomach 4 hours later. The urine and faeces excreted in those 4 hours did not contain any significant amount of radioactivity. Apart from the stomach, large quantities of radioactivity were found in decreasing order in the plasma, kidneys, whole blood, liver, lungs, and heart. Twenty-four hours after dosing, 60-65% and 35-40% of the radioactivity were found in the urine and faeces, respectively; at a dose of 10 mg/kg bw, these figures were about

75-80% and 20-25%, respectively. The biological half-life of disappearance from rat tissues was in the order of 10 hours after dosing 50 mg/kg bw. There did not appear any significant accumulation of the radioactive compound in any of the tissues (Smi69b).

Clopidol did not accumulate in fat of cattle: after feeding with food containing 500 mg clopidol/kg, the concentration clopidol in fat after 28 days was 0.2-0.9 mg/kg (Ken80). Seven days after feeding chickens with 125 mg ³⁶Cl-clopidol/kg food, the amount of radioactivity in liver, plasma, and muscles was 1-4 x 10⁻⁶ that of the original amount (0.01-0.04 ppm). No samples were taken at earlier time points; no half-life times were calculated (Smi69a).

6 Effects and mechanism of action

Human data

The committee did not find data on effects in humans due to exposure to clopidol.

Animal data

The committee did not find data on the potential irritation and sensitisation of clopidol.

An oral LD₅₀ of 18,000 mg/kg bw has been reported in rats (Pli70; only abstract available). According to unpublished information, LD₅₀ values were greater than 8000 mg/kg bw for rats, rabbits, and guinea pigs (ACG99).

Citing unpublished studies, it was stated that no adverse effects on growth, appearance, mortality, terminal haematological and clinical chemical examinations, final body and organ weights, gross and microscopic examinations of major organs, and tumour incidence were seen in rats fed 15 mg/kg bw /day, for 2 years. Also in dogs fed 5 mg/kg bw/day, for 2 years, there were no adverse effects (no more details presented) (ACG99).

Clopidol was well tolerated at 500 mg/kg food by lambs, and no toxic effects were observed in doses of 900 and 1800 mg/kg food. The length of the study was not given. A significant increase in leukocytes and lymphocytes was observed in all doses compared with controls. No significant changes were observed in the blood proteins, serum transaminases, liver, spleen, or kidneys (Sev72; only abstract available).

Mutagenicity and genotoxicity

In vitro, clopidol did not induce gene mutations when tested with and without induced rat liver metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 *hcr* at concentrations up to 5000 µg/plate (Oht80). Clopidol produced negative results in a differential killing-rec assay using *B. subtilis* strains H17 (rec⁺) and M45 (rec⁻), an indicator test for DNA damage (Oht80).

The committee did not find data from mutagenicity or genotoxicity tests in mammalian cell systems.

Results from *in vivo* genotoxicity studies were published in Chinese and available from a very brief English abstract without presenting more data than are following below. In what is probably a dominant lethal assay, male mice were dosed daily with 100 mg clopidol/kg bw for 5 consecutive days and then mated with 6 groups of females serially for 6 weeks. In the third group of females, the number of living embryos for each female was lower (10.7) and the number of dead embryos significantly higher (1.2) when compared with controls (12.2 and 0.044, respectively). Its 'mutagenic index' was significantly increased (10.1 vs. 3.4). Further findings were increases in the frequency of micronucleated polychromatic erythrocytes (6.5% vs. 2.6%) in fetal mice liver 18 hours after treatment with a dose of 160 mg/kg clopidol, in polyploids (3% vs. 0.4%) and sperm abnormalities (5.34% vs. 3.28%) after a dose of 50 mg/kg bw, and in the number of sister chromatid exchanges per cell (4.27, 5.23, and 5.96, respectively, vs. 2.88) at doses of 10, 30, and 160 mg/kg bw, respectively (Bao92).

The committee concluded that clopidol may have mutagenic activity, but this should be investigated further.

Reproduction toxicity

Results from (what is probably a) teratogenicity study were published in Chinese and available from a very brief English abstract without presenting more data than are following below. Groups of pregnant Wistar rats received oral doses of clopidol of 0, 4, 20, 100, and 200 mg/kg bw on gestational days 6 through 15. At 200 mg/kg bw, maternal body weights were decreased. The two highest doses decreased the pregnancy rate (p<0.01)*. At 200 mg/kg bw, fetal effects including

* The committee notes that since treatment was started with animals that were pregnant already for 6 days, treatment cannot have been the cause of decreased pregnancy rates (unless something else was meant by this term).

decreased body weight and length ($p < 0.05$) and extra ribs and delayed ossification of the sternum (in 15/16 fetuses) were reported. The percentage fetal malformations was higher than that in controls. At 100 mg/kg bw, a decreased average litter weight was found (Jia99).

Citing unpublished studies, it was stated that clopidol had not induced adverse effects on fertility, gestation, viability, lactation, or on teratogenicity in rats and rabbits (no more data/details presented) (ACG99).

The committee concluded that clopidol may have effects on the development of offspring of rats, but this should be investigated further.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for clopidol in the Netherlands is 10 mg/m³, 8-hour TWA.

Existing occupational exposure limits for clopidol in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find data on the toxicokinetics of clopidol following dermal or inhalation exposure. After oral intake, clopidol was absorbed and excreted rapidly. In rabbits, 90% or more of single or repeated radiolabelled doses of 16 mg/kg bw were excreted in the urine within 24 hours after dosing, a hydroxylated product and its *O*-glucuronide accounting for almost half of the radioactivity. In rats, orally given 10 or 50 mg/kg, about 65 and 80%, respectively, of the radioactivity administered was excreted in the urine, the remainder in the faeces.

The committee did not find data on the toxic effects of clopidol in humans.

Experimental animal data are limited to poorly reported information on systemic effects (including reproduction toxicity) following oral exposure. LD₅₀ values for rats, rabbits, and guinea pigs were greater than 8000 mg/kg bw. No effects were observed in rats and dogs fed daily doses of 15 or 5 mg/kg bw, respectively, for 2 years; in rats, there was no increase in tumour incidences. No effects on reproduction were reported in rats and rabbits given doses unknown to the committee in one study, but in another rat study, administration of doses of 100 or 200 mg/kg bw during organogenesis caused decreased fetal weights and decreased fetal weights and sizes, increased incidence of fetal malformations, and decreased maternal body weights, respectively.

Clopidol did not induce mutations or DNA damage in bacteria. *In vivo*, positive results were found for several endpoints in one poorly reported study.

The committee considers the database on clopidol too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC value.

Recommendations for research

The committee recommends to further investigate the mutagenicity/genotoxicity and reproduction toxicity of clopidol.

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Annex

Occupational exposure limits for clopidol in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	reference ^b
	ppm	mg/m ³				
the Netherlands - Ministry of Social Affairs and Employment	-	10	8 h			SZW03
Germany - AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain - HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	-	10	8 h			Arb02
USA - ACGIH	-	10	8 h	TLV	A4 ^c	ACG03b
- OSHA	-	15 ^d ; 5 ^e	8 h	PEL		ACG03a
- NIOSH	-	10 ^d ; 5 ^e	10 h	REL		ACG03a
	-	20 ^e	15 min			
European Union - SCOEL	-	-				EC03

^a S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

^b Reference to the most recent official publication of occupational exposure limits.

^c Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

^d Total dust.

^e Respirable fraction.