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On centrophenoxine's safety concerns:

Centrophenoxine, also known as meclofenoxate, is a nootropic that is used as a prescription drug in some European countries and in Japan, for example. Centrophenoxine has been marketed under the brand names Lucidril, Centrophenoxin, Cerutil and Helfergin, just to name a few.

Clinical applications of centrophenoxine have included psychiatric diseases, amyotrophic lateral sclerosis, migraine, and brain injury, among others.

It has also been widely used for off-label purposes in the life extension and performance enhancement circles.

According to the United Nations' *Consolidated List of Products - Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments* (12th issue, 2005, full list, can be found [here](#); 14th issue, 2009, new data 2005-2008 can be found [here](#); update to the 14th issue (WHO), 2010, can be found [here](#)), there's no official information on meclofenoxate/centrophenoxine having ever been banned, withdrawn, severely restricted, or not approved by governments due to safety concerns.

Still, concerns regarding centrophenoxine's safety have been raised, specifically regarding the possibility of inducing birth defects. These concerns derive from the reported effects of dimethylethanolamine (DMAE) on embryonic development.¹ Centrophenoxine is the ester of DMAE and 4-chlorophenoxyacetic acid (pCPA) and is converted into DMAE and pCPA.

In this article we examine those concerns by looking at 1) the evidence of DMAE's effects on embryonic development, 2) the conversion of centrophenoxine to DMAE, and 3) the relevant studies of safety of centrophenoxine.

DMAE's effects on embryonic development

The main study that gave rise to the concerns regarding DMAE's effects involved early stage mice embryos (gestational day 9) exposed to DMAE for 26 hr in embryo culture and which showed neural tube anomalies and altered development of craniofacial structures in a dose-dependent manner.¹ In another *in vitro* study using sea urchin embryo cultures as a screen for developmental neurotoxicants, DMAE elicited dysmorphology beginning at the mid-blastula stage, with anomalies beginning progressively later as the concentration of DMAE was lowered.²

A 2002 review of the toxicological literature on [DMAE and some of its salts and esters](#), including centrophenoxine, prepared for the US National Institute of Environmental Health

Sciences, also reported the following (regarding inhaled DMAE):

“Leung et al. (1996)³ reported sporadic, inconsistent alterations in gestational parameters including significant decreases in viable implants per litter, percentage live fetuses/litter, and litter size in rats exposed to 10 ppm (40 mg/m³; 41 mmol/m³) and a significant decrease in the percentage of male fetuses in rats exposed to 30 ppm (110 mg/m³; 1.20 mmol/m³), while IUCLID (1997) reported no treatment-related effects on any reproductive parameters including pre- and postimplantation losses or sex ratio changes. Inhaled DMAE induced variations in skeletal parameters in the fetuses of pregnant Fischer 344 rats exposed to 10 (40 mg/m³; 0.41 mmol/m³) to 100 ppm (370 mg/m³; 4.10 mmol/m³) DMAE on gestation days 6 to 15. However, a consistent pattern was lacking, resulting in a NOAEL (no observed adverse effect level) for embryo-fetal toxicity and teratogenicity of 100 ppm (370 mg/m³; 4.10 mmol/m³) or greater. A NOAEL for maternal toxicity was estimated at 10 ppm (40 mg/m³; 0.41 mmol/m³).”

It should be noted that these studies are difficult to translate to relevant oral doses of DMAE as a supplement, and that despite these studies, DMAE remains on the market as both a prescription drug and dietary supplement in many countries around the world, with no known reported incidents of human birth defects.

Centrophenoxine’s hydrolysis into DMAE

Given that the concern for Centrophenoxine is based on its conversion to DMAE, it’s worth looking at the rate and pharmacodynamics for the physiological conversion of centrophenoxine into DMAE and pCPA.

The hydrolysis of centrophenoxine in the human plasma has been studied *in vitro* at 25°C.⁴ In that study, centrophenoxine was found to decompose rapidly in human plasma via spontaneous hydrolysis as well as esterase-induced hydrolysis. The spontaneous hydrolysis appeared to be inhibited by some components in human plasma. The authors concluded that their results indicated that “a significant amount of meclofenoxate that enters the circulation could be hydrolyzed before it penetrates into the brain.”⁴

An animal study performed *in vivo* used radioactively labeled DMAE, pCPA and centrophenoxine (labeled either on its DMAE moiety or its pCPA moiety) to determine centrophenoxine’s fate (*=labelled; MF-DMAE*: MF labelled by DMAE*; MF-PCPA*: MF labelled by PCPA*). It was shown that, in the blood, the concentration of MF-DMAE* was high at 1 and 5 min after intravenous administration, but was null thereafter, showing that centrophenoxine was taken up quickly by multiple organs (see table 1).⁵ DMAE* by itself was also rapidly taken up by multiple organs, although in a slightly different pattern (the most striking difference being the uptake by the brain and spinal cord, see discussion below). But the concentration of MF-PCPA*, on the other hand, remained high in the blood 1 hr after administration, when MF-DMAE* is no longer observed in the blood. This suggests that there is indeed a fast hydrolysis of centrophenoxine. DMAE was also rapidly transported into the liver where much of it is known to be metabolized.⁶

TABLE II. Rise and Fall of Radioactivity Appeared on Autoradiograms

Organs	MF-PCPA*				MF-DMAE*					PCPA*		DMAE*		
	1 min	5 min	1 hr	4 hr	1 min	5 min	1 hr	2 hr	4 hr	24 hr	5 min	5 min	1 hr	4 hr
Brain	###	###	+	±	##	##	##	##	##	##	-	-	±	±
Spinal Cord	###	###	+	±	##	##	##	##	##	+	-	-	±	±
Blood	###	###	###	##	##	##	-	-	-	±	###	+	-	±
Lung	###	##	##	+	##	##	+	##	##	##	##	+	+	##
Spleen	±	+	+	+	+	##	+	+	+	##	+	+	+	##
Bone Marrow	±	+	+	+	##	##	+	##	+	##	+	##	##	##
Stomach (Content)	±	+	+	+	###	###	##	##	##	+	-	-	##	##
Small Intestines (Content)	±	+	+	+	±	##	##	##	+	##	+	+	##	##
Large Intestines (Content)	-	±	±	±	-	##	+	+	±	±	-	±	±	±
Liver	±	+	+	+	±	##	+	##	+	##	+	+	+	##
Adrenal Cortex Medulla	###	##	##	+	±	±	+	+	##	##	##	-	+	##
Submaxillary Gland	##	+	+	+	###	###	###	###	###	###	+	###	###	###
Kidney	##	##	##	##	+	###	###	###	##	###	###	##	##	###
Urinary Bladder	-	+	###	###	-	###	###	###	###	##	##	###	###	##
Bone	+	+	+	+	###	###	###	+	±	+	+	##	±	+
Muscle	##	##	+	+	###	##	+	+	+	+	+	+	+	+

###: highest radioactivity, ##: higher activity, +: high activity, ±: low activity and -: no activity

Table 1 - From: Miyazaki H, et al. Chem Pharm Bull (Tokyo) 1976; 24: 763-9.⁵ MF: meclofenoxate hydrochloride; DMAE: β -dimethylaminoethanol hydrochloride; PCPA: p-chlorophenoxyacetic acid; *=labelled; MF-DMAE*: MF labelled by DMAE*; MF-PCPA*: MF labelled by PCPA*.

Another study assessed the pharmacokinetic properties of centrophenoxine *in vivo* by doing a time-course evaluation of the concentration of pCPA in human plasma (they didn't measure DMAE). They found that the concentration of pCPA in the plasma increased rapidly and peaked 2h after intake, and then also declined rapidly, again suggesting a fast hydrolysis.⁷

Therefore, these data indicate that centrophenoxine is hydrolyzed relatively quickly, and that both the pCPA molecule and DMAE are also quickly absorbed by multiple organs. This means that, in the context of pregnancy, only a portion of the administered dose of centrophenoxine would have the chance to reach the embryo or fetus intact or as DMAE.

Centrophenoxine's effects on embryonic development

Importantly, centrophenoxine itself has been studied for its effects on fetal development. In experiments with rats assessing teratogenicity of centrophenoxine, the data suggest that it actually reduces teratogenicity in Wistar rats. Prenatal treatment with centrophenoxine lead to a significant increase of the weight of the fetuses of rats. Also, centrophenoxine caused, in continuous series of generations, an increase of fertility which resulted in a higher number of offsprings.⁸ Another study found a protective function against malformations (clefts) by

centrophenoxine.⁹

Centrophenoxine was also tested for its possible action on influencing the prenatal changes induced by cyclophosphamide, which has teratogenic effects, and chloramphenicol, which has embryotoxic and weak teratogenic effects. Apart from the weight of the fetuses, centrophenoxine had no influence on the effects of cyclophosphamide, whereas for chloramphenicol, an increase of the toxic effect could be observed with centrophenoxine.¹⁰ In a different study, centrophenoxine was shown to weaken the teratogenic effect of cyclophosphamide.¹¹

A study assessing the effect of centrophenoxine on lung development showed that centrophenoxine administered to pregnant guinea pigs had inhibitory effects on the activity of cholinephosphotransferase in the adults, but not in the fetuses; when injected directly into the fetuses, centrophenoxine induced a decrease in the activity of cholinephosphotransferase. It was concluded that centrophenoxine injected to pregnant animals does not seem to affect the fetus directly.¹²

Centrophenoxine's side-effects

Centrophenoxine has been used in multiple human studies. The vast majority of those studies were done before the 90s in Europe (mostly Germany, Bulgaria, France, Italy, Poland, Russia...). Since only big journals or publishers have their archives from the 60s/70s/80s digitized, many of those studies are not accessible, and often there's not even an abstract.

Still, there were several human studies that assessed centrophenoxine's side-effects.

There was one study that described an activation of epileptic seizures by centrophenoxine in patients with subacute and chronic cerebral circulatory disturbances caused by atherosclerosis (no information on dose, data from abstract, no full text available).¹³ In another study, centrophenoxine was administered at a dose of 3000 mg/day throughout 12 months to 10 people with a mean age of 64. Mild gastric pain that disappeared after 20 minutes was reported by 4 patients, and 5 Patients complained of a very small increase in jitteriness. This study also analyzed the bone marrow and a number of indicators of renal and hepatic function; it was shown that there were no other adverse effects after this long-term treatment with an extremely high daily dosage.¹⁴

With lower doses of centrophenoxine, no side effects were reported. Centrophenoxine did not induce any adverse changes at doses of: 2000mg/day for 8 weeks in 50 people (25 men, 25 women) over the age 60 (average age: 77 years) suffering from dementias of medium level;¹⁵ 1520 mg/day for 3 months in elderly people with senile dementia of Alzheimer type of mild to moderate intensity;¹⁶ 1250 mg/day for 8 weeks in 31 patients with cerebral insufficiency;¹⁷ 900 mg/day 4 weeks in 51 patients with head injury whose blood pressure and pulse were monitored, and blood, liver function, and urine tests were made (increased thirst was reported by one patient);¹⁸ 600-1200 mg/day for 6-12 weeks in 11 subjects with tardive dyskinesia or dystonia whose excessive salivation, lacrimation, anorexia, diarrhea, hypotension, bronchospasm or aggravation of psychiatric symptoms were monitored;¹⁹ 200mg, single-dose,

in 24 healthy volunteers aged 22-30 years who were monitored for the occurrence of excitement, insomnia, lassitude, and headache, and for vital signs and laboratory tests (hematology, blood biochemistry, hepatic function, and urinalysis).⁷

Therefore, these data indicate that, at doses commonly used by humans, centrophenoxine seems to be well tolerated.

There are a few published contraindications for centrophenoxine.

Given centrophenoxine's effects in activating epileptic seizures, mentioned above, it is contraindicated for individuals with convulsive disorders such as epilepsy.

Centrophenoxine can inhibit mammary secretion and should therefore not be taken by women who are breastfeeding.^{20,21}

As with all cholinergics, since centrophenoxine can increase the levels of choline,²² it can potentially interact with cholinergic and anticholinergic drugs.

Due to the increased levels of choline, individuals with trimethylaminuria, renal disease, liver disease, depression, and Parkinson's disease may be at risk of adverse effects.²³

Centrophenoxine is also contraindicated for people with severely high blood pressure.

Conclusion

Regarding concerns about birth defects, while there are some studies in animal models that show teratogenic effects of DMAE administered to pregnant mothers or to fetus's directly, none of these studies involved oral dosing to the mother. Moreover, there are no known reports of human teratogenicity despite DMAE's widespread, multi-decade, multi-country use as both a prescription drug and dietary supplement. DMAE is a widely available and used dietary supplement throughout the US and much of the world. It is also still used as a pharmaceutical drug (Deanol), where it is not considered contraindicated for women of childbearing age. It is avoided during pregnancy and breastfeeding, not because of evidence of danger but lack of adequate safety data.

Studies on centrophenoxine in animal models have not shown evidence of teratogenicity, and similarly there are no known reports in humans despite widespread, multi-decade, multi-country use as both a prescription drug and a dietary supplement.

Despite the widespread use of centrophenoxine (and DMAE), for many purposes, across many population types, for over four decades, self administered as supplements and prescribed by doctors, there appear to be no known reports of birth defects in humans or recalls of either of these chemicals, as drugs or supplements, from any of the countries regulating their usage.

However, large scale trials and observational studies would be required to demonstrate the safety of centrophenoxine in pregnant women. As no such trials are currently underway

centrophenoxine should not be used during pregnancy or breastfeeding.

Regarding other safety concerns as a supplement, other than for the contraindications listed above, it is generally considered well tolerated.

A follow up article on the efficacy of Centrophenoxine is in process.

References

We reviewed 179 available published articles in research centrophenoxine. The ones referenced below were the most relevant for this article on safety concerns.

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