# PERMITTED DAILY EXPOSURE FOR METHYLCOBALAMIN

## 1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Methylcobalamin have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

## 2. INTRODUCTION:

Methylcobalamin (mecobalamin, MeCbl, or $MeB_{12}$) is a cobalamin, a form of vitamin $B_{12}$. It differs from cyanocobalamin in that the cyano group at the cobalt is replaced with a methyl group. Methylcobalamin features an octahedral cobalt(III) centre and can be obtained as bright red crystals. From the perspective of coordination chemistry, Methylcobalamin is notable as a rare example of a compound that contains metal–alkyl bonds. Nickel–methyl intermediates have been proposed for the final step of methanogenesis.

Methylcobalamin is equivalent physiologically to vitamin $B_{12}$ and can be used to prevent or treat pathology arising from a lack of vitamin $B_{12}$ intake (vitamin $B_{12}$ deficiency).

Methylcobalamin is also used in the treatment of peripheral neuropathy, diabetic neuropathy, and as a preliminary treatment for amyotrophic lateral sclerosis.

Methylcobalamin that is ingested is not used directly as a cofactor, but is first converted by MMACHC into cob(II) alamin. Cob (II) alamin is then later converted into the other 2 forms, adenosylcobalamin and Methylcobalamin for use as cofactors. That is, methylcobalamin is first dealkylated and then regenerated.

## 3. IDENTITY OF THE ACTIVE SUBSTANCE:

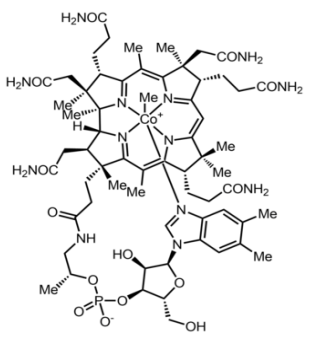
**IUPAC name:** carbanide; cobalt(3+)

**Chemical Abstract Services (CAS) Registry Number:** 13422-55-4

**Molecular Weight:** 1344.40 g/mol g·mol−1

**Chemical Formula:** $C_{63}H_{91}CoN_{13}O_{14}P$

**Molecular Structure:**



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## 4. HAZARDS IDENTIFIED:

| CATEGORIZATION: | | | |
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| **TOXICITY** | **YES** | **NO** | **UNKNOWN** |
| **Genotoxicant** | - | - | √ |
| **Carcinogen** | - | √ | - |
| **Reproductive/Developmental Toxicant** | - | √ | - |
| **Highly Sensitizing potential** | - | √ | - |

| SUMMARY OF HAZARD IDENTIFICATION: | |
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| **Pharmacodynamics data** | It works by functioning in the production of a compound called myelin, which covers and protect nerve fibers. Methylcobalamin rejuvenates the damaged neuron. Without enough Methylcobalamin, myelin sheath does not form properly due to which nerve fibers suffers and people experience irreversible nerve damage. An intrinsic factor made in the stomach, must be present in the intestinal tract to allow its proper absorption. People lacking this factor show vitamin $B_{12}$ deficiencies such as pernicious anemia (a slow and insidious process that can end in death. Pernicious anemia in fact means 'leading to death'). Methylcobalamin is used as a cofactor in methionine transferase enzyme, an enzyme which converts aminoacid homocysteine to methionine via folate cycle. |
| **Pharmacokinetics data** | Methylcobalamin can be administered orally, parenterally and intranasal. Methylcobalamin binds with an intrinsic factor and form a complex which is absorbed in distal ileum. Its half-life is 6 days. The absorption is mediated by very specific receptor mediated transport system. It is distributed to every cell of the body upon binding to Transcobalamine II, a B-globulin carrier protein and is stored in the liver in an amount of 300-500 microgram. It is eliminated through bile. Methylcobalamin nasal sprays bioavailability is 9%. |
| **Acute Toxicity** | Vitamin $B_{12}$ is usually nontoxic even in large doses; however, mild transien diarrhea, peripheral vascular thrombosis, itching, transitory exanthema, urticaria, feeling of swelling of the entire body, anaphylaxis, and death have been reported. Although allergic reactions to vitamin $B_{12}$ have generally been attributed to impurities in the preparation, a few patients have reacted positively to skin testing with purified Cyanocobalamin. |
| **Repeated Dose Toxicity (Chronic Toxicity)** | **LD50 Oral (mouse):** > 5000 mg/kg. Vitamin $B_{12}$ is generally non-toxic, even at higher doses. Mild, transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching, transitory exanthema, a feeling of swelling of entire body, pulmonary edema and congestive heart failure in early treatment stages, anaphylactic shock and death have been observed after vitamin $B_{12}$ administration. |
| **Carcinogenicity** | Long term studies in animals examining the carcinogenic potential of any of the vitamin $B_{12}$ formulations have not completed to date. There is no evidence from long-term use in patients with pernicious anemia that vitamin $B_{12}$ has carcinogenic potential. Pernicious anemia is known to be associated with an increased incidence of stomach carcinoma; however, this malignancy has been attributed to the underlying cause of pernicious anemia and has not been found to be related to treatment |

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| | with vitamin $B_{12}$. |
| **In vivo/In vitro Genotoxicity Studies** | No data available. |
| **Reproductive/Developmental Toxicity** | **Use in pregnancy:** No adverse effects have been reported with ingestion of normal daily requirements during pregnancy. Although vitamin $B_{12}$ is an essential vitamin and requirements are increased during pregnancy, it is currently unknown whether the nasal spray form can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The nasal spray form should be given to a pregnant woman only if clearly needed, as it is considered a pregnancy category C drug in this form. Sufficient well-controlled studies have not been done to this date in pregnant women.<br>**Use in lactation:** Vitamin $B_{12}$ has been found distributed into the milk of nursing women in concentrations similar to the maternal blood vitamin $B_{12}$ concentrations. No adverse effects have been reported to date with intake of normal required doses during lactation. In women who are pregnant, excessive blood levels of Vitamin $B_{12}$ & there derivatives have been associated with an increased risk of autism in their children.<br>**Vitamin $B_{12}$ is excreted into human breast milk:** In the first 48 hours after delivery, mean colostrum levels were 2431 pg/ml & then fell rapidly to concentration comparable to those of normal serum. One group of investigators also observed very high colostrum levels, ranging from 6-17.5 times that of milk. Milk: plasma ratios are approx. 1.0 during lactation. Reported milk concentration of $B_{12}$ varies widely. |
| **Highly Sensitizing Potential** | Since the Cobalamin molecule contains a cobalt atom, taking large amounts of Vitamin $B_{12}$ (in either oral or injectable forms) may result in rashes and itching in people with a history of cobalt allergy. While these reactions are not likely to be dangerous, they can result in an uncomfortable itchy rash. |

| IDENTIFICATION OF CRITICAL EFFECTS: | |
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| **Sensitive Indicator of an adverse effect seen in non-clinical toxicity data** | No any adverse effect seen in non-clinical toxicity data. |
| **Clinical therapeutic and adverse effects** | **Clinical Therapeutic Dosage:** The dosage for clinical effect is 1500-6000 mcg per day. No significant therapeutic advantage appears to occur from dosages exceeding this maximum dose.<br>**Adverse effect:** At a very high dose, Methylcobalamin causes blood clots, diarrhea, paresthesia, rhinitis, ataxia, pruritis and allergic reactions. People with polycythemia should consult with a physician before taking this therapy. This drug can be applied as a topical paste on the skin without any adverse reaction. Sometimes intravenous injection of this drug leads to hypersensitivity reactions and end up to anaphylactic shock. In some cases, hypokalamia and thrombocytosis has occurred in the patient while treating megaloblastic anemia with Methylcobalamin.<br>Convulsions, followed by cardiac or respiratory failure, have been described in mice given 1.5-3 mg/kg body weight of Vitamin $B_{12}$; |

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| | Clinical signs were not thought to be due to hypersensitivity. |

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| **NOAEL/LOAEL** | 120 mg/kg/day (Maximum daily dose) considered as NOAEL value. |

| **APPLICATION OF ADJUSTMENT FACTORS:** | | |
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| **F1:** Extrapolation between species | 1 | No extrapolation taken, direct maximum daily dose taken. |
| **F2:** Inter Individual Variability | 10 | Used for differences between individuals in the human population. |
| **F3:** Duration of Toxicity (Repeat Dose Toxicity) | 10 | Reference data not available, hence worst factor considered. |
| **F4:** Severe Toxicity (1-10) | 1 | No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed |
| **F5:** NOAEL or LOAEL (10 if LOAEL) | 5 | NOAEL value is selected (Maximum daily dose is selected in mg/kg/day). |
| **PK Correction** | For PDE calculation no pharmacokinetic correction was carried out | |

| **CALCULATION** | |
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| **PDE Calculation** | $\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$<br>$= \frac{\text{120 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$<br>= 2.4 mg/day |

**5. REFERENCES:**


- https://en.wikipedia.org/wiki/Methylcobalamin
- http://www.altmedrev.com/archive/publications/3/6/461.pdf
- https://austinpublishinggroup.com/pharmacology-therapeutics/fulltext/ajpt-v3-id1076.php
- https://pubchem.ncbi.nlm.nih.gov/compound/Cyanocobalamin#section=Human-Toxicity-Excerpts