# SIDS INITIAL ASSESSMENT PROFILE

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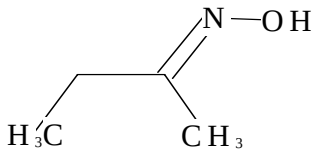
| **CAS No.** | 96-29-7 |
| **Chemical Name** | 2-Butanoneoxime (MEKO) |
| **Structural Formula** |  |

## SUMMARY CONCLUSIONS OF THE SIAR

### Identity

There is only one major isomer for 2-butanoneoxime (MEKO), which is trans/anti. During the oximation process, the size of the ethyl group and its rotation favors formation of primarily (>99%) trans/anti isomer which is stable.

### Human Health

Data indicate that MEKO is rapidly absorbed from the gastrointestinal tract and skin, after which it is rapidly metabolized and excreted.

Three acute oral studies in rats conducted according to GLP resulted in the following LD50s : 1) 930 mg/kg in males, and 1620 mg/kg in females, 2) 2326 mg/kg (males and females), and 3) greater than 900 mg/kg (males and females). The dermal LD50 for rabbits was between 1000 and 1800 mg/kg bw. Specifically, in one study, no lethality was observed at 1000 mg/kg bw and in a second study, all rabbits died at 1800 mg/kg. The rat LC50 (4-hr) was > 4,800 mg/m$^3$ (no rats died) in a well-conducted acute inhalation study. Following a single oral dose of MEKO to rats in an acute neurotoxicity study, transient effects characterized as motor incoordination were seen at treatment levels of 300 and 900 mg/kg but not at 100 mg/kg.
MEKO has been shown to be slightly irritating to the skin but is severely irritating to the eye. MEKO is an animal skin sensitizer. However, no sensitization to MEKO in workers has been reported.

Repeated inhalation and oral dose toxicity studies have shown MEKO to have effects on the red blood cells (effects on blood parameters indicative of hemolytic anemia and compensatory hematopoiesis, as well as extramedullary hemosiderosis in the spleen) and on olfactory epithelium. In several of these studies, the effects have been demonstrated to be reversible.
In a 13-week inhalation study in CD-1 mice, a NOAEL of 3 ppm (10.8 mg/m$^3$) was established based on olfactory effects in a small area of tissue in the nose at doses of 10 ppm (36 mg/m$^3$) and higher. These effects were minimal at lower doses and moderately severe at higher doses. After cessation of exposure, the effects showed reversal to varying degrees, depending on dose. (It should be noted that the nasal morphology and respiratory physiology of the rodent is different from humans such that higher local exposure of the olfactory epithelium is expected to occur in rodents as compared to humans at equivalent airborne concentrations of MEKO.) A shorter (4-week) inhalation study, also in CD-1 mice, showed a slight increase in methemoglobin levels as well as increased spleen and adrenal weights, resulting in a NOAEL of 100 ppm (360 mg/m$^3$) and a LOAEL of 400 ppm (1440 mg/m$^3$). With repeated inhalation exposure in rats for 4 weeks, a NOAEL (hematology) of 25 ppm (90 mg/m$^3$) and a LOAEL of 100 ppm (360 mg/m$^3$) have been identified for the effects of MEKO on blood parameters, including increased levels of

methemoglobin. A second inhalation study in rats also found effects on the blood, but the results were confounded by a viral infection in the treated and control groups.

Gavage and drinking water studies with durations of 4 and 13 weeks have been conducted with rats and one 13-week drinking water study has been conducted in mice. A common effect observed in these studies is hematological effects such as anemia. Degeneration of the nasal epithelium was seen in both drinking water studies. In one 13-week gavage study with rats, a LOAEL of 25 mg/kg bw/day was determined based on hemolytic anemia seen even at the lowest treatment level. At higher doses in this study, anemia was fairly serious. Other effects observed in this study include dose-related effects on spleen and liver weights and compensatory hematopoeisis. In another 13-week gavage study in rats (designed to evaluate subchronic neurotoxicity), hematologic effects (including increased methemoglobin levels) were seen at doses of 40, 125, and 400 mg/kg bw/day. In a 13-week drinking water study with Fischer rats, the NOAEL was reported as 312 ppm (about 25 mg/kg bw/day). A LOAEL of 625 ppm (50 mg/kg bw/day) was set based on erythrotoxicity observed at this and higher doses. Degeneration of the nasal epithelium was observed at 2500 ppm (200 mg/kg bw/day) and higher. A 4-week gavage study in Fischer rats found effects on the hematopoietic system at 20 mg/kg bw/day and above, with a NOAEL of 4 mg/kg bw/day. A second 4-week gavage study in rats found no significant hepatic peroxisome proliferation. However, a LOAEL of 250 mg/kg bw/day was established for this study based on increased hepatic glutathione. A 13-week drinking water study in mice resulted in methemoglobinemia, responsive Heinze body anemia, increased spleen weights, and haematopoietic effects. Degeneration of the nasal olfactory epithelium was observed in addition to hyperplasia of the transitional epithelial lining of the urinary bladder. The NOAEL from this study was at 625 ppm (110 mg/kg bw/day) based on hyperplasia of the epithelial lining of the urinary bladder in males at 1250 ppm (200 mg/kg bw/day).

In the 13-week neurotoxicity study in rats described above, dose levels of 40 and 125 mg/kg bw/day did not elicit any consistent or apparent treatment-related change in neurobehavioral function or nervous system structure. However, transient neurobehavioral changes (cage removal, handling, posture, gait, arousal, salivation, approach response, rearing responses, and aerial righting) occurred at doses of 400 mg/kg bw/day. They were noted immediately after dosing, and had resolved by the next day. No progressive long term, irreversible neurotoxic changes were associated with MEKO administration (as was seen with the positive control agent).

In the 2-year inhalation oncogenicity study in rats (with interim analysis, sacrifices at 3, 12, 18 months), similar effects on blood parameters were seen at 375 ppm (1300 mg/m$^3$) at 3 months and 12 months but not at 18 months in males or at 26 months (both sexes). Effects to the spleen (increased organ weight, extramedullary hematopoiesis, and hemosiderosis) were seen at 375 ppm (1300 mg/m$^3$). Spleen weights were increased in both sexes at 3 and 12 months, 18 months (females only), but not at 26 months. The histopathological effects persisted at the same time points as the changes in spleen weights. Splenic histopathology could not be accurately determined at termination due to spontaneous leukemia. In the 374 ppm (1346 mg/m$^3$) group, testes were 82 percent heavier than the control group at study termination. There was a treatment-exaggerated increase in incidence of corneal dystrophy and opacities; these changes were much more severe at 374 ppm (1346 mg/m$^3$). At termination, there were increased red/tan discolorations and nodules/masses in the liver in the 374 ppm group. Other non-cancer effects in the liver included increased incidence of basophilic foci and hepatocellular vacuoles, adenomas, and spongiosis hepatis. Degenerative nasal effects were also observed at 12 and 18 months.

In the 2-year inhalation oncogenicity study in mice, the effects on the blood were less clear. There was an increase in methemoglobin at 12 months only in males. Other blood parameters were affected to varying degrees. Degenerative effects observed in the olfactory epithelium resulted in a LOAEL of 15 ppm (54 mg/m$^3$).

The type and pattern of hematological effects from the 2-year inhalation study at a relative high dose (1,360 mg/m$^3$) suggests that the degree of these blood effects is less severe when exposures to similar quantities of MEKO occur over an extended time period as is with inhalation exposure compared with oral gavage exposures. The repeated-dose studies also indicate that the rat is more sensitive to the hematotoxic effects of MEKO compared with mice.

The genotoxicity potential of MEKO has been well investigated both in-vitro (gene-mutation, chromosome aberration, and DNA studies) and in-vivo (gene mutation, chromosome aberration studies, and DNA study). Six reverse bacterial mutation assays conducted by several methods in standard bacterial strains did not find a mutagenic response in the presence or absence of rat liver activating enzymes. A single reverse mutation bacterial assay conducted by the preincubation method reported a mutagenic response in only tester strain TA1535 and only in the presence of high (not standard) levels of hamster liver activating enzymes. A mouse lymphoma study found evidence of mutagenic activity in the absence of rat liver activating enzymes but not following rat liver enzyme activation. *In vitro* studies for chromosome aberrations, SCE, unscheduled DNA Synthesis (UDS) were negative. *In vivo* Drosophila (for sex-linked recessive mutations), and micronucleus studies showed no evidence of genotoxicity. An *in*

*vivo* rat study to investigate the potential for MEKO to produce DNA adducts found no evidence of adduct formation with MEKO. The weight of evidence suggests that MEKO is likely to be non-genotoxic.

In carcinogenicity inhalation studies with MEKO with doses up to 374 ppm in rats and 375 ppm in mice showed MEKO to be a carcinogen to the liver only. In rats, these tumors developed late in life and did not appear to affect survival. .

In a 2-generation study with doses up to 200 mg/kg bw/day MEKO, no effects on reproduction were seen. No compound related effects on reproductive organs (sperm samples and vaginal samples inclusive) could be found in the subchronic studies in rats and mice Together these results suggest that there is no specific effect on the reproductive system. In developmental studies, the highest dose was 600 mg/kg bw/d in rats and 40 mg/kg bw/day in rabbits. MEKO showed no developmental effects even at maternally toxic doses (NOAEL (rat) < 60 mg/kg bw/day; NOAEL (rabbit) = 14 mg/kg bw/day).

**Environment**

MEKO is a liquid, with a water solubility of 110 g/l and a vapor pressure of 3.5 hPa at 20 °C. The octanol/water partition coefficient was Log Kow = 0.65 at 25 °C and the Henry's Law Constant is 1.04 x $10^{-5}$ atm-$m^3$/mol using the bond estimation method.
Photodegradation in the atmosphere occurs by reaction with OH radicals, with a half life of 7.2 days. The fugacity distribution modeling according to Mackay Level III indicates soil (40.8 %), air (9.2%), and water (50.0 %) to be the favored compartments in a scenario where equal amounts are released to soil, water, and air. In a scenario where 100 % of the releases are to air, the majority of MEKO (62.7%) remains in the air, 17 % goes to water, and 19.9 % goes to soil. Results of a hydrolysis test showed that after 4 days at pH 7, 14 % hydrolysis was observed. MEKO hydrolyzes to form methyl ethyl ketone and a hydroxylamine salt. MEKO was found to be inherently biodegradable in one test, whereas it was not biodegradable by a second test on inherent biodegradability. The measured BCFs in fish generally range from 0.5 to less than 2.5, indicating low or no bioaccumulation potential.

The reported toxicity data for MEKO in fish and daphnia show values greater than 100 mg/L. In the 72-hour algal toxicity study, the EC50s are reported as 11.6 mg/L (growth rate) and 6.09 mg/L (biomass). NOECs from this study are 2.56 mg/L (growth rate) and 1.02 mg/L (biomass).

**Exposure**

Worldwide production is estimated to be 10000 - 20000 tonnes per year. The major application is as anti-skinning agent for alkyd coating resins for use in solvent based paints. The concentration of MEKO in these products is typically 0.3 % (range 0.1% – 0.8 %). The next main applications are as a blocking agent for isocyanates (used as a raw material for powder coatings) and as a reactant in the manufacturing of oxime-silanes (used as cross linkers for one-component neutral cure silicone sealants). In case of oxime-crosslinkers and sealants thereof, the level of MEKO is generally less than 1.0%.

## RECOMMENDATION

The chemical is a candidate for further work

## RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

MEKO possesses properties indicating a hazard for the environment and exposure assessment (production/formulation

sites and end use products) is recommended as post-SIDS work. MEKO is clearly a chemical with hazardous properties (slightly irriatant to skin, severely irritant to eyes, and sensitizing to animals) and measures should be taken to control exposures to acceptable levels. The potential for hazards to human health and exposure to consumers warrant an in-depth exposure assessment as post-SIDS work to estimate consumer exposure. In addition, the U.S. will evaluate the 2-year inhalation carcinogenicity study and mechanistic data for MEKO.