

Is BOP more hazardous than other peptide reagents ???

BOP has been used as coupling reagent in peptide synthesis in both solution and solid-phase strategies, promotes peptide cyclization and other lactamization, especially β -lactam formation, used to effect various amidification reaction, selective esterification and nucleotidic coupling.

Although BOP is widely used in laboratories, this compound is not accepted for industrial applications, due to statement that HMPA, a side product of BOP is carcinogenic. This statement is based on IARC (International Agency for Research on Cancer) report [1] that when administered by inhalation of HMPA (up to 4000 ppb) during 8 months, the compound induced nasal tumors in rats of both sexes. No nasal tumor were found in rats exposed to 50 ppb. (In addition, in the same report, it was stressed that there is no adequate data available to evaluate the carcinogenicity of HMPA in humans).

These data of human suspected carcinogenicity migrate from report to report (up to Ninth Annual IARC Report at 2001[2]), ignoring the opposite facts.

For instance, in 1975 a major exposure study with rats was initiated at DuPont Haskal laboratories (HMPA was used as solvent in DuPont Kevlar production) [3]. In another report (1995) it was note that HMPA had been studied **for many years and no unusual toxic effects had been reported**. This compound has no hazard to the workers, the community and the customers [4], although the some animal carcinogenicity can be exist [3].

Prior to the DuPont observations, the only other known report of tumors associated with exposure to HMPA was a long-term feeding study by Kimbrough. While lung tumors were observed, the results of this study were inconclusive because the tumor incidence among HMPA exposed rats was not greater than among the control rats [5].

In 1997 the researchers from Department of Pharmaceutical Science, Philadelphia College of Pharmacy and Science conducted the research of mitogenic responses of rat nasal epithelium to HMPA inhalation exposure. They have shown that for 3 ppm dose, there was **no evidence of cytotoxicity** in the anterior nose of rats [6].

According to IARC, HMPA was placed in Group 2B chemicals (possible human carcinogen) together with methylene chloride and 1,4-dioxane [7].

Another important feature of biological activity of chemical compounds is their **mutagenic** action.

In 1969 it was published that HMPA produced mutagenic effects in fruit flies (*Drosophila melanogaster*) [8].

In 1985 it was shown that HMPA has a low capacity for delayed mutations. HPLC analysis of DNA reacted with [14 C] HMPA exhibits no methylation of DNA bases, especially of guanine [9].

However, studies of the effects of HMPA on human [10] and mice [11] chromosomes showed no greater frequency of HMPA induced chromosomal aberrations when compared with controls.

Doubtless, HMPA is known to have a variety of toxic effects on laboratory animals, but this is comparable to ones of other common reagents, using in peptide chemistry.

Toxicity (LD₅₀ – lethal dose 50 percent kill) [12]:

	intraperitoneal, mouse	administration onto skin, rabbit
HMPA	1600 mg/kg	2600 mg/kg
DMF	650 mg/kg	4720 mg/kg
Piperidine	50 mg/kg	320 mg/kg

Teratogenicity (TDLo – lowest published toxic concentration) [12]:

oral, rat

HMPA	2430 mg/kg
DMF	1820 mg/kg
Piperidine	900 mg/kg
TMU	500 mg/kg

In addition, HBTU and HATU are coupling reagent, using currently for production of pharmaceutical peptides [13]. During the coupling reaction TMU is produced as main side product. This compound is known as cytotoxic [14,15], mutagenic [16,17], teratogenic [18], but this fact is not an obstacle for using HBTU, HATU, TBTU (and other TMU-based reagents) in pharmaceutical and chemical industries.

PyBOP was proposed as an alternative for BOP. The authors [15] claimed that the side product tris(pyrolidino)phosphine oxide is less toxic than HMPA. But according to article [19], PyBOP (and other Py-reagents: PyAOP) contains pyrrolidine, compound known as mutagen [12] and more toxic [12] than HMPA [LD₅₀ – 420 mg/kg (intraperitoneal, mouse)].

Summary

BOP (as HMPA) is not more dangerous than common reagents, using in peptide syntheses: DMF, piperidine, HBTU, HATU, TBTU, dichloromethane, acetonitrile.

LITERATURE

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